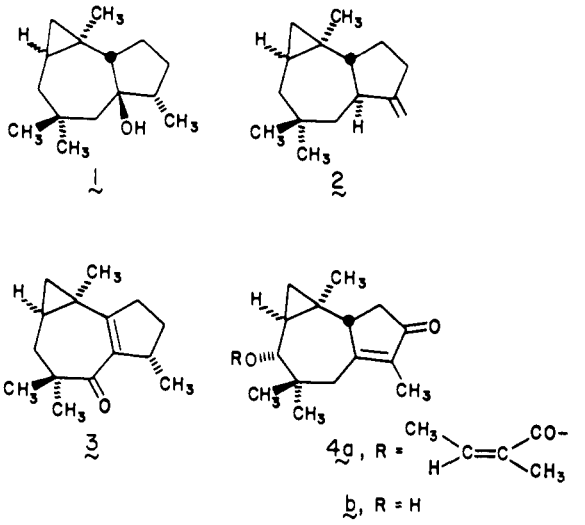
Total Synthesis of the Marine Sesquiterpenes Dactylol and Africanol. De novo Construction of a Cyclooctanoid Natural Product from Cycloheptane Precursors

Leo A. Paquette* and Won Hun Ham

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received November 10, 1986*

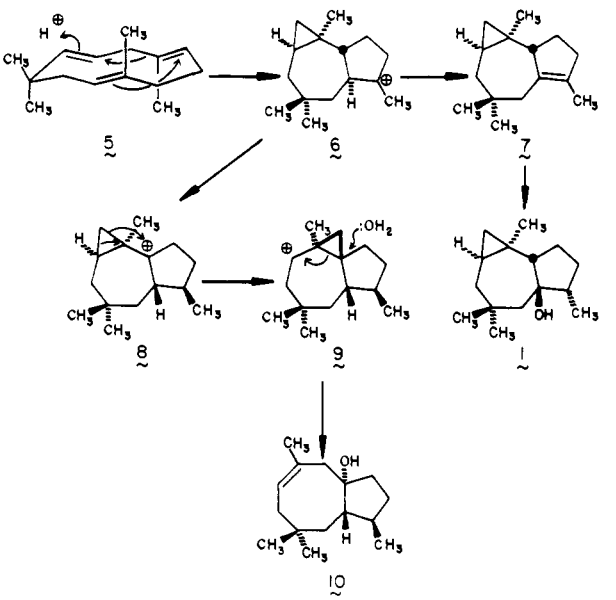
Abstract: The total synthesis of the marine sesquiterpenes africanol (**1**) and dactylol (**10**) from bicyclo[5.1.0]octane precursors is described. The enone **12** was ketalized and cyclopropanated. Removal of the blocking group, aldol condensation with acetaldehyde, and controlled 1,2 reduction provided the allylic alcohol **15a**. Ortho ester Claisen rearrangement of this alcohol furnished carboxylic acid **16**, which was converted predominantly to **25** by Friedel–Crafts cyclization of its acid chloride and acid-catalyzed dithioketalization. Following treatment with Raney nickel, the crucial epoxidation step occurred preferably from the α face to deliver **29**. This intermediate has previously been transformed into dactylol (**10**). Diisobutylaluminum hydride acted on **42** with high stereoselectivity to deliver chiefly the allylic alcohol **43**, ortho ester Claisen rearrangement of which was completely stereocontrolled. This pathway to **49a** made it convenient to achieve cyclization to **50**. This tricyclic ketone underwent Dibal reduction preferentially from the β face to give **54**. Conversion of **54** to africanol (**1**) was achieved by controlled epoxidation, dissolving metal reduction of the epoxy mesylate, and catalytic hydrogenation. Other aspects of the synthetic strategy are also discussed.

The sesquiterpene africanol (**1**) was isolated in 1974 by Tursch and co-workers[1] from the soft coral *Lemnalia africana*. The structure of this interesting tricyclic alcohol, established by means of X-ray analysis,[2] serves as the prototype of the africane group of natural products that presently also includes $\Delta^{9(15)}$-africanene (**2**),[3] africanone (**3**),[4] and 8β-angeloyloxy-senoxyri-4-en-3-one



(**4a**).[5] The two ketones are not of marine origin. Shirahama has proposed that **1** is biosynthetically derived from humulene, which in its CT conformer **5**[6] undergoes initial acid-catalyzed closure to the 9-africyl cation (**6**).[7] Proton loss and subsequent hydration

Scheme I



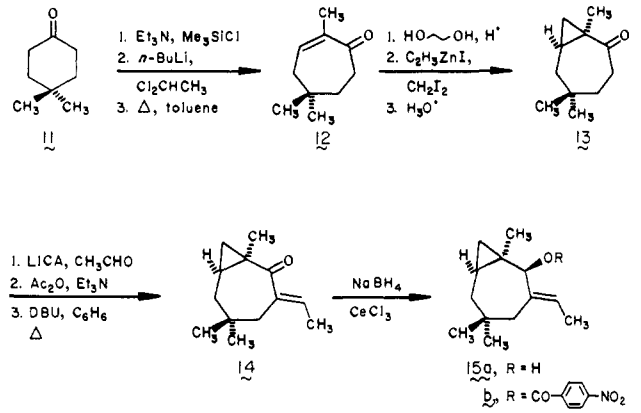
presumably occur to provide **1** (Scheme I).

More recently, the possibility has been entertained that **6** may find it possible to experience 1,2-prototropic shift and formation of the 6-africyl cation (**8**).[8] Should the neighboring cyclopropane ring in **8** subsequently enter into 1,2-migration in the manner illustrated, arrival at dactylol (**10**) becomes possible. This irregular isoprenoid alcohol was characterized by Schmitz in 1978 as a substance produced by the Caribbean sea hare *Aplysia dactylomela*.[9,10] The outlined mechanistic proposal, whose feasibility has recently been demonstrated by Hayasaka and co-workers starting from **1**,[8] denotes for the first time that cyclooctanoid natural products can be produced by isomerization of suitable cycloheptane precursors.

(1) Tursch, B.; Braekman, J. C.; Daloze, D.; Fritz, P.; Kelecom, A.; Karlsson, R.; Losman, D. *Tetrahedron Lett.* **1974**, 747.
(2) Karlsson, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 2609.
(3) (a) Kashman, Y.; Bodner, M.; Finer-Moore, J. S.; Clardy, J. *Experientia* **1980**, *36*, 891. (b) Braekman, J. C.; Daloze, D.; Tursch, B.; Hull, S. E.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Ibid.* **1980**, *36*, 893.
(4) Dartayet, G. H.; Catalan, C. A.; Retamar, J. A.; Gros, E. G. *Phytochemistry* **1984**, *23*, 688.
(5) Bohlmann, F.; Zdero, C. *Phytochemistry* **1978**, *17*, 1669.
(6) Shirahama, H.; Osawa, E.; Matsumoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 3208.
(7) Shirahama, H.; Ohfune, Y.; Misumi, S.; Matsumoto, T. *J. Synth. Org. Chem., Jpn.* **1978**, *36*, 569.
(8) Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985**, 873.
(9) Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719.
(10) Synthesis: Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123. Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343.

0002-7863/87/1509-3025$01.50/0

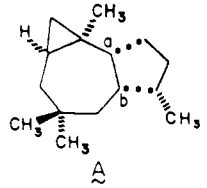
Scheme II



Although **1** and **4** (as **4b**) have been prepared by Lewis acid-catalyzed rearrangement of humulene-9,10- and 4,5-epoxides, respectively,[11,12] no de novo synthesis of a representative africane had been reported when our efforts were initiated.[13] Herein we describe stereocontrolled total syntheses of africanol (**3**)[14] and 8-epiafricanol. In addition, a route to epoxide **29**[15] that has previously been converted in two steps to **10**[8] is detailed.

Results and Discussion

The Africane Ring System. In planning construction of the tricyclic hydroazulenoid framework present in the africanes, the decision was made to adopt a strategy that would invove fusion of a functionalized cyclopentane ring onto a preformed bicyclo[5.1.0]octane nucleus. Although a related tactic has been described on two earlier occasions,[16a,b] no cyclopropane ring was involved in either study.[16c] Quite naturally, particular concern had to be focused on the five contiguous chiral centers in **1**. For synthetic purposes, there exists the option of generating the first C–C bond at site a or at site b (see A). In either case, it was



A

imperative that all complications stemming from potential cyclopropylcarbinyl cation intervention (as in **8**) be avoided. Both of these avenues will be explored in turn, shown to be devoid of this potential source of structural rearrangement, and demonstrated to be adaptable to the stringent stereochemical requirements of the target molecules.

With these considerations in mind, ketone **13** was viewed as the logical medium-ring precursor (Scheme II). Given the ready availability of 4,4-dimethyl-2-cyclohexenone[17] and its reported quantitative hydrogenation to **11**,[18] our efforts were concentrated on suitable ring expansion of this intermediate. The silyl enol ether of **11**, prepared by the method of House and co-workers,[19] was treated with chloromethylcarbene resulting from reaction of 1,1-dichloroethane and *n*-butyllithium.[20] Thermolysis of the resulting halogenated silyloxycyclopropane in toluene solution led to cycloheptene **12** which was directly ketalized. This adaptation of Conia's methodology proved particularly efficient (71% overall).[21,22]

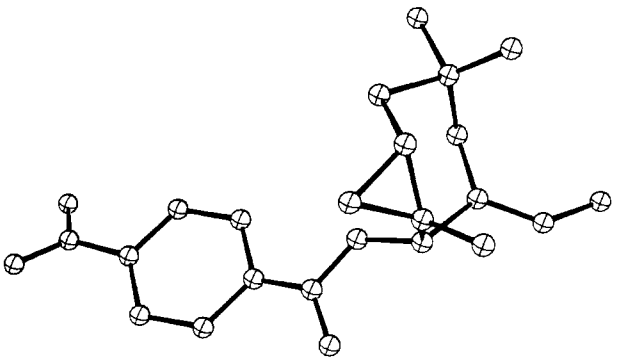


Figure 1. ORTEP diagram of **15b** with hydrogens omitted for clarity (courtesy of Prof. I. Bernal and Dr. J. D. Korp, University of Houston).

Importantly, double bond migration did *not* occur during conversion to the ethylenedioxy derivative. Accordingly, the stage was set for lateral fusion of the cyclopropane ring. The use of ethylzinc iodide and diiodomethane[23] proved particularly serviceable. Following hydrolytic removal of the blocking group, **13** was isolated in 92% yield.

The enolate anion of **13** entered readily into aldol condensation with acetaldehyde. Although acid-catalyzed dehydration[24] of the resulting β-hydroxy ketone proceeded satisfactorily when small amounts were involved, the process did not scale up well. A simple solution to this obstacle consisted of acetylation and subsequent β-elimination of acetic acid with DBU in hot benzene.[25] Only **14** resulted (71% overall), the anti stereochemistry of which was evident from the appearance of its olefinic proton at δ 6.91 in $CDCl_3$ solution. The downfield displacement of this signal owes its origin to positioning within the deshielding region of the neighboring carbonyl group.[24,26] No evidence was found for formation of the syn isomer (olefinic proton absorption anticipated at ca. δ 5.5).

With **14** in hand, our attention was next focused on the stereochemistry of reduction at the carbonyl site. This issue was of importance because of our impending plan to transfer the chirality introduced at the newly installed carbinol center to the olefinic side chain by Claisen rearrangement. Following treatment with the Luche reagent,[27] alcohol **15a** was produced almost exclusively. Because the relative configurational relationships in **15a** could not be convincingly resolved by NMR techniques, *p*-nitrobenzoate **15b** was prepared and subjected to X-ray crystal structure analysis.[28] The conformation adopted by this ester (Figure 1)

(11) Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, 4835.

(12) (a) Mlotkiewicz, J. A.; Murray-Rust, J.; Murray-Rust, P.; Parker, W.; Riddell, F. G.; Roberts, J. S.; Sattar, A. *Tetrahedron Lett.* **1979**, 3887. (b) Bryson, I.; Mlotkiewicz, J. A.; Roberts, J. S. *Ibid.* **1979**, 3891.

(13) Earlier unsuccessful attempts have been detailed in Widener, R. K. Ph.D. Thesis, Indiana University 1977.

(14) Preliminary report: Paquette, L. A.; Ham, W. H. *Tetrahedron Lett.* **1986**, 2341.

(15) Preliminary report: Paquette, L. A.; Ham, W. H.; Dime, D. S. *Tetrahedron Lett.* **1985**, 4983.

(16) (a) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081. (b) Rigby, J. H.; Wilson, J. Z. *Ibid.* **1984**, *106*, 8217. (c) Fusion of a six-membered ring to a functionalized bicyclo[5.1.0]octane derivative has been deployed in a successful total synthesis of jatropholones A and B: Smith, A. B., III; Liverton, N. J.; Heib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Org. Chem.* **1985**, *50*, 3239.

(17) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399.

(18) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1347.

(19) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(20) Blanco, L.; Amice, P.; Conia, J.-M. *Synthesis* **1981**, 289.

(21) The closely related procedure of Saegusa would not result in direct introduction of the 2-methyl group: (a) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073. (b) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth.* **1980**, *59*, 113.

(22) For a comparably abbreviated method for introducing a 3-methyl group with concomitant one-carbon ring expansion, see: Hiyama, T.; Mishima, T.; Kitatani, K.; Nozaki, H. *Tetrahedron Lett.* **1974**, 3297.

(23) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2269.

(24) Yanami, T.; Miyashita, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 525.

(25) (a) Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398. (b) Kido, F.; Kitahara, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1236.

(26) (a) Crandall, J. K.; Arrington, J. P.; Hen, J. *J. Am. Chem. Soc.* **1967**, *89*, 6208. (b) Paquette, L. A.; Eizember, R. F. *Ibid.* **1967**, *89*, 6205.

(27) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(28) We thank Professor Ivan Bernal and Dr. James D. Korp of the University of Houston for performing this structural analysis.

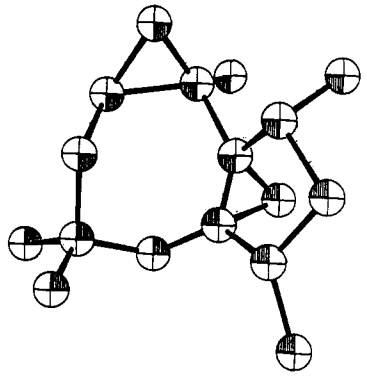
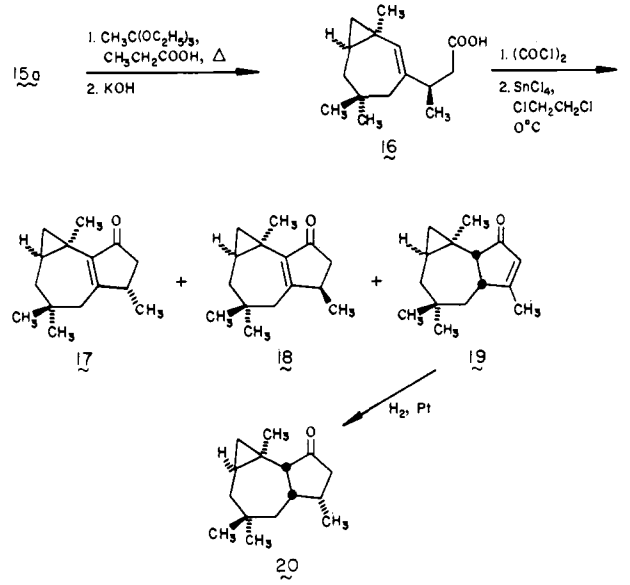
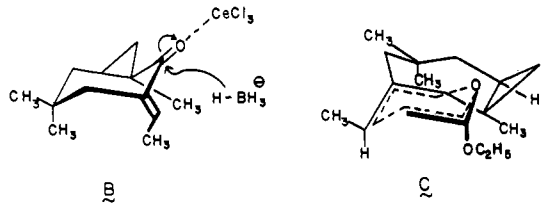


Figure 2. Perspective drawing of **24** derived from the X-ray coordinates with hydrogens omitted for clarity (courtesy of Dr. J. P. Springer, Merck, Sharp, and Dohme).

Scheme III

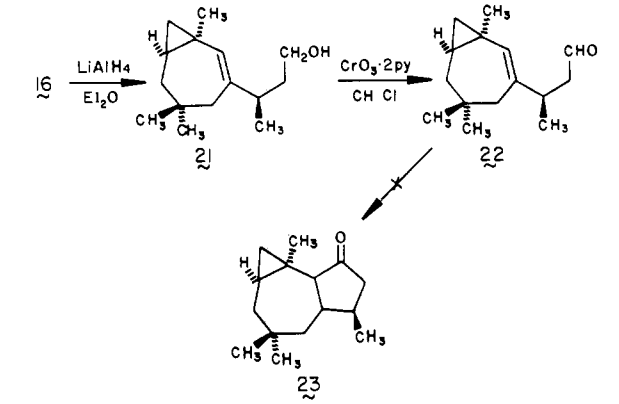


suggests that the delivery of hydride occurs as illustrated in B for steric reasons.

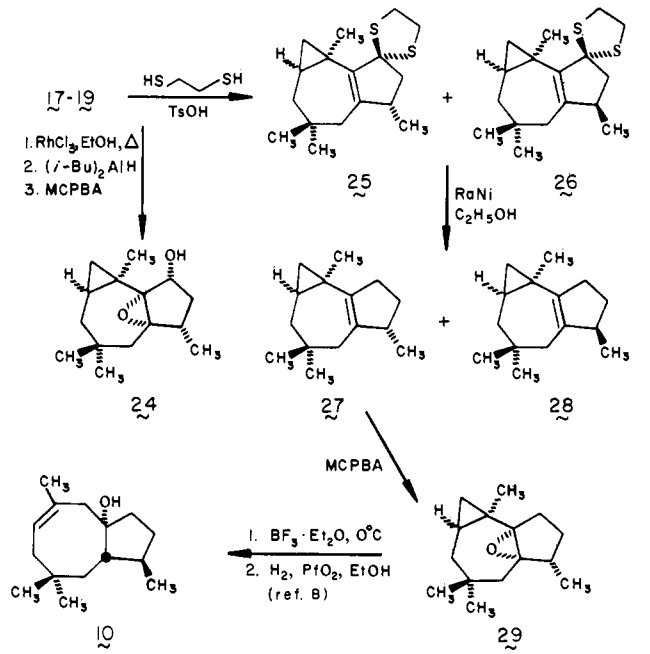


Associated with the triethyl orthoacetate variant of the Claisen rearrangement within **15a** are two limiting transition states. Of these, the chairlike conformation C gave a priori indication of being clearly favored.[29] At the experimental level, the usual conditions for this transformation as applied to **15a** delivered a stereochemically homogeneous ester (72%) whose saponification furnished **16** (Scheme III). The totality of the chirality transfer is noteworthy. The configuration of the side chain methyl group, inferred from the preceding stereoelectronic considerations, is seen to be proper in relation to dactylol (**10**) but opposite to that present in africanol (**1**).

Scheme IV



Scheme V



The next goal, cyclization with generation of a functionalized five-membered ring, was at the outset pursued from two directions. In the first, carboxylic acid **16** was transformed into its acid chloride. Exposure of this intermediate to aluminum chloride in carbon disulfide solution resulted in formation of a dark reaction mixture from which only **19** could be isolated (34%). The stereostructure assigned to **19** is based on consideration of its ^{1}H NMR spectrum and examination of molecular models. Furthermore, catalytic reduction of **19**, anticipated to proceed with β delivery of hydrogen and formation of **20**, does indeed lead to a saturated tricyclic ketone possessing methyl absorptions closely comparable to those exhibited by africanol.

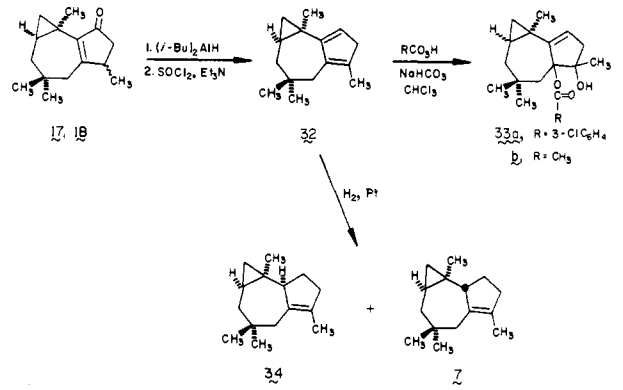
The preceding results were disappointing but not totally unexpected.[30] Alternate recourse to stannic chloride in anhydrous 1,2-dichloroethane at 0 °C gave rise in 96% yield to a mixture of **17** (12%), **18** (24%), and **19** (64%). The excellent yield of cyclization products in this instance, when combined with the efficiency of the subsequent rhodium trichloride-promoted isomerization,[31] proved to be an especially attractive avenue for the preparation of **17**. More specifically, exposure of the three-component mixture to the transition-metal salt in hot ethanol induced double bond isomerization that eventuates in domination by **17**

(29) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, Chapter 8. (b) Considerable elegant use has been made in the recent past of the Claisen rearrangement in various synthetic undertakings by the Ziegler group at Yale. For selected examples, see: Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181. (c) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278. (d) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

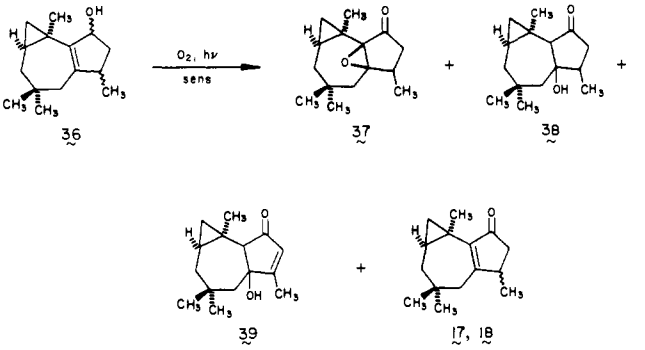
(30) See, for example: Büchi, G.; Macleod, W. D., Jr.; Padilla, O. *J. Am. Chem. Soc.* **1964**, *86*, 4438.

(31) (a) Grieco, P. A.; Hishizawa, M.; Marinovic, N. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (b) Andrieaux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (c) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.

Scheme VI



Scheme VII



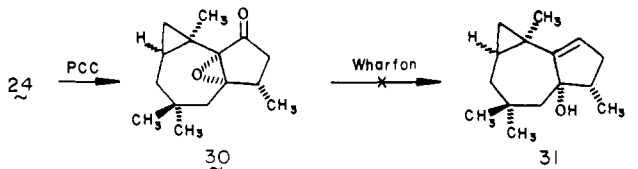
to the extent of 68%. The proportion of **19** is thereby drastically reduced to only 3%. Proper stereochemical distinction between **17** and **18** was made by conversion of **17** to epoxy alcohol **24** and X-ray analysis of this highly crystalline substance (Figure 2).[32]

Alternative possible construction of a stereochemically defined annulated cyclopentanone ring by rhodium(I)-catalyzed intramolecular hydroacylation[33] also appeared attractive. To assess this option, aldehyde **22**, the requisite substrate, was prepared conveniently from **16** in two steps (Scheme IV). When all attempts to effect the cyclization of **22** in the presence of various rhodium(I) complexes were recognized to lead exclusively to recovery of unreacted aldehyde, our attention became entirely focused on the utilization of **17**.

Synthesis of Dactylol. To our delight, chromatographic separation of the enones **17–19** proved not to be necessary, since dithioketalization of the mixture gave only **25** and **26** in an 83:17 ratio (Scheme V). Initially, the relative stereochemical assignments to **25** and **26** were made tentatively on the basis of the apparent thermodynamic bias of the secondary methyl group for the α environment, as encountered earlier. Unequivocal definition of stereochemistry was readily achieved by sequential Raney nickel desulfurization and epoxidation. The overwhelmingly major product proved to be **29**.

The successful elaboration of **29** from **16** requires no chromatography until completion of the epoxidation step. As an important point of stereochemical reference, the peracid can be seen to prefer approach to the π bond in **27** predominantly from the α face to deliver **29**. Its ^{1}H NMR spectrum was identical with that provided by Professor Matsumoto.[8] The facility with which **29** undergoes Lewis acid-catalyzed isomerization with cleavage of both three-membered rings and conversion to dactylol (**10**) has been earlier detailed by the Matsumoto group.[8] Thus, it is now possible to view 5/8-fused sesquiterpenes such as **10** as being usefully accessible from hydroazulenoid precursors.

Experiments Directed toward Elucidation of the Chemical Reactivity of the Annulated Five-Membered Ring. With **24** conveniently available, we became interested in determining if the derived ketone **30** would be capable of Wharton rearrangement.[34]

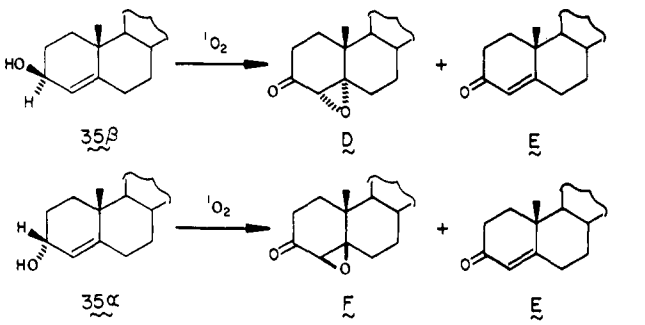


Our long-range objective was to study **30** as a model for the related β-epoxy β-alcohol, a prelude to arriving at africanol (**1**) in two additional steps. Unfortunately, ketone **30** proved resistant to conversion to allylic alcohol **31**, even after heating with hydrazine hydrate at temperatures as high at 118 °C.[35] Although we were well aware that a change in relative configuration might allow for possible operation of the desired transformation, this avenue was not pursued.

In contrast, the ready conversion of **17**/**18** into the cyclopentadiene **32** could be achieved without difficulty (Scheme VI). The doubly unsaturated A ring in this acid-sensitive hydrocarbon is recognized to be present in artabsin,[36] the major sesquiterpene lactone constituent[37] of *Artemisia absinthium*.[38] All attempts to realize regiospecific epoxidation of the more highly substituted double bond in **32** was met with exceedingly rapid conversion to hydroxy carboxylates. *m*-Chlorobenzoate **33a** and acetate **33b** are exemplary of the observed chemical behavior. The ease of formation of these end products is believed to be the combined result of exhaustive alkyl substitution of the intermediate oxirane and the presence of an immediately adjoining olefinic center.

As anticipated, controlled hydrogenation of **32** proceeds at its less substituted double bond to give **34** and **7** (ratio 73:19) in addition to a small amount of an unknown byproduct. Of the two hydroazulenes formed, the known[1] natural product **7** was easily recognized from the characteristic upfield portion of its ^{1}H NMR spectrum. No synthesis of **7** has previously been documented.

In 1963, Nickon and Mendelson reported on two very interesting observations.[39] These workers noted that photooxygenation of Δ^4-cholesten-3β-ol (**35**β) in the presence of hematoporphyrin as sensitizer produced the 4α,5-epoxy ketone (D, 75%) along with a lesser amount of enone E (10%). Under analogous conditions, the 3α-ol **35**α gave rise to the 4β,5-epoxy ketone (F, 50%) and E (10%). Given this insight, our hope was that **36** would behave analogously and thereby make available a particularly expeditious



(32) We thank Dr. James Springer of the Merck, Sharp, and Dohme Research Laboratories for performing this structural analysis.

(33) (a) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281. (b) Campbell, R. E., Jr.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824. (c) Larock, R. C.; Oertle, K.; Potter, G. F. *Ibid.* **1980**, *102*, 190. (d) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257. (e) Sakai, K.; Ishiguro, Y.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* **1984**, *25*, 961.

(34) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S. *Ibid.* **1961**, *26*, 4781.

(35) For a useful modification of the Wharton rearrangement, see: Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984**, *106*, 4558. This modification was not utilized because of its acetic acid requirement and the acid sensitivity of our substrate. At the highly elevated temperatures employed, substrate polymerization and conversion to diene **32** was observed.

(36) Vokac, K.; Samek, Z.; Herout, V.; Sorm, F. *Coll. Czech. Chem. Commun.* **1960**, *25*, 1492.

(37) Beauhaire, J.; Fourrey, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1982**, 861.

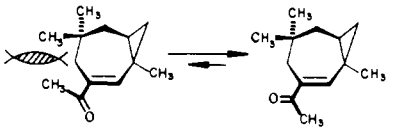
(38) Kelsey, R. G.; Shafizadeh, F. *Phytochemistry* **1979**, *18*, 1591.

(39) Nickon, A.; Mendelson, W. L. *J. Am. Chem. Soc.* **1963**, *85*, 1074.

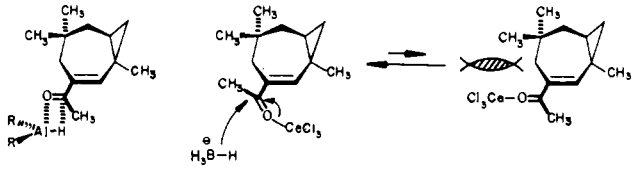
route to **37**. Neglected by us in this comparison was the fact that the double bond in **36** is appreciably more congested on both of its surfaces than the corresponding site of unsaturation in either isomer of **35**. The reaction of **36** with singlet oxygen was examined under conditions similar to those used by Nickon and Mendelson. However, a myriad of products was formed (Scheme VII). The desired epoxy ketone **34** was isolated chromatographically but only in 7.7% yield. Two somewhat more polar compounds tentatively identified as **38** (12%) and **39** (16%) also resulted. Not unexpectedly, 22% of the enone pair **17**/**18** was recovered. The complexity of this process obviously did not lend itself to our synthetic objectives and was not further investigated.

Synthesis of Africanol. Structural information culled from the X-ray analyses of **1**, **15b**, and **24**, coupled with independent examination of Dreiding models for related molecules, indicated the bicyclo[5.1.0]octane ring common to this group to be essentially locked into a single preferred conformation.[40] Our expectations were that this topological feature could be translated into stereoselective chemical transformations under the proper circumstances. To test this proposition, ketone **13** was converted by way of keto ester **40** and α,β-unsaturated ester **41** to acetyl derivative **42** (Scheme VIII). The selection of **42** was predicated on the results of molecular mechanics calculations[41] that demonstrated conformer **42b** to be at least 0.7 kcal/mol more stable than **42a**. The indicated methyl–methyl interaction evidently destablizes the structural assignment present in **42a**.

Central to our synthetic plan for arrival at africanol was the availability of an efficient method for reducing the carbonyl group in **42** stereoselectively to allylic alcohol **43**. In view of the mechanism by which aluminum hydride reagents add to carbonyl compounds,[42] we considered it most plausible that the attack of Dibal on **42b** would be relegated to "below-plane" (see G) because



42a **42b**

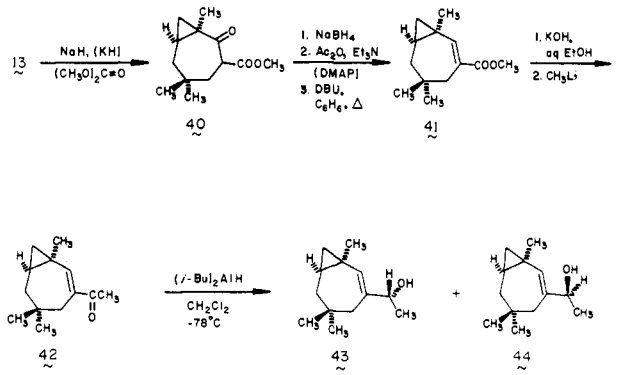


G **H** **I**

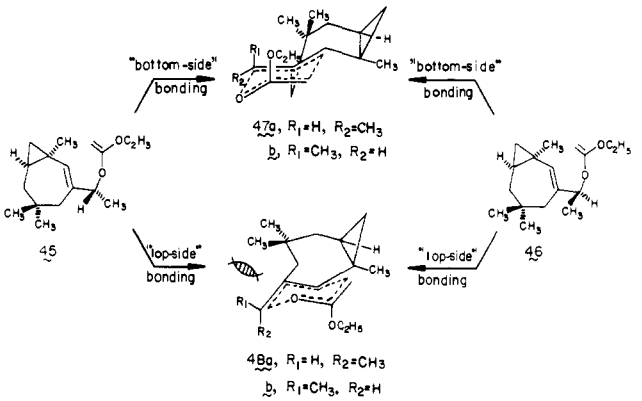
of steric shielding on the alternate surface by one of the geminal methyl groups. In point of fact, the end product of this reaction conducted at −78 °C was an 88:12 mixture of two easily separable carbinols, the major constituent of which was formulated as the desired **43** for the above reasons.

Exposure of **42** to cerium trichloride-doped sodium borohydride,[27] a reagent system noted for prior coordination of the lanthanide to the electronegative carbonyl oxygen,[43] was expected to favor conformer H in order to minimize CH_3–$CeCl_3$ interactions (see illustration). Attack by BH_4^- from below in order to avoid related steric complications should consequently lead to predominant formation of **44**. When **42** was treated in this manner, the resulting **43**/**44** ratio was substantially in favor of **44** (ratio 1:2). Thus, respectable stereoselectivity can indeed be realized without difficulty in the 1,2 reduction of **42**.

Scheme VIII



Scheme IX



The reader should recognize that the preceding analysis is speculative in that it necessarily deals with small energy differences. In H, the cerium ion is indicated to be coordinated anti to the methyl group. In I, a distorted version of the same stereorelationship is intended. Nonetheless, one could argue with reasonable experimental support that $CeCl_3$ coordinates syn to the methyl in both conformers, constitutes an equilibrium situation similar to that for **42a**/**42b**, and is subject to facially selective reduction commensurate with the product distribution.

The correctness of our configurational assignments to **43** and **44** surfaced quickly. The projected ortho ester Claisen rearrangement of **43** is seen to be governed by two chairlike transition-state options (Scheme IX).[29,44] The first **47a**, which involves C–C bond formation trans to the cyclopropane ring, does *not* experience the 1,3-diaxial interaction so clearly evident in **48a**. Accordingly, thermal activation of **45** was predicted with reasonable confidence to proceed predominantly via "bottom side" bonding. Since **49a** was actually formed exclusively (Scheme X), the level of chirality transfer in this instance is seen to be excellent.

The comparable handling of **46** proved informative. In this instance, esters **51a** and **52a** were formed in a 1:1 ratio. Evidently, the nonbonded steric interactions that develop in transition-state **48b** induce a level of destabilization entirely comparable to that arising from 1,3-diaxial interactions in **47b**.

Following proper introduction of the third chiral center as in **49**, the derived acid chloride was cyclized by means of alicyclic Friedel–Crafts chemistry.[30,45] The success of this step rested on the expectation that the intermediate tricyclic carbocation would undergo β-elimination to form the conjugated ketone at a rate faster than hydride migration leading to the cyclopropylcarbinyl cation. The latter event would likely lead to unwanted expansion

(40) Compare: (a) Birladeanu, L.; Harris, D. L.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 6387. (b) Detty, M. R.; Paquette, L. A. *Ibid.* **1977**, *99*, 821. (c) Cope, A. C.; Moon, S.; Park, C. H. *Ibid.* **1962**, *84*, 4843. (d) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III *J. Org. Chem.* **1982**, *47*, 3960. (e) Danheiser, R. L.; Morin, J. M., Jr.; Solaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066.

(41) We thank Dr. M.-A. Poupart for performing these calculations in the Departmental Computer Graphics Facility.

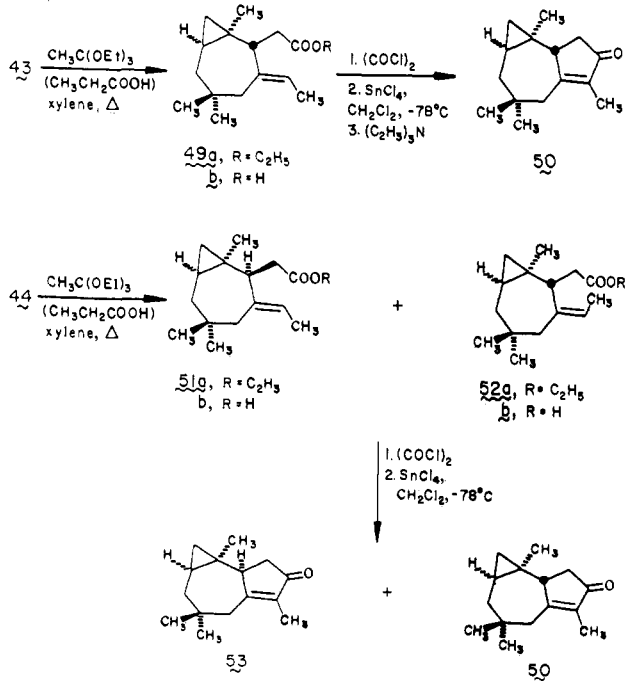
(42) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; Chapter 2.

(43) Inagaki, F.; Miyazawa, T. *Prog. Nucl. Magn. Reson. Spectrosc.* **1980**, *14*, 67.

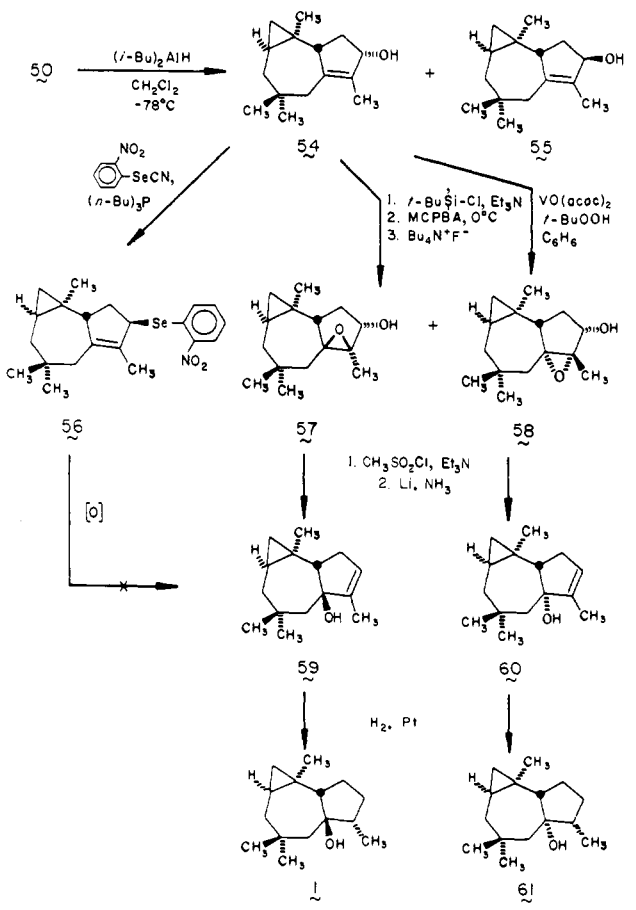
(44) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829.

(45) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.

Scheme X



Scheme XI



of the seven-membered ring via cyclopropane rupture.[8] As anticipated, the stereochemically homogeneous cyclopropane-substituted ketone **50** was produced in good yield when use was made of stannic chloride in dichloromethane solution at −78 °C. Of course, **52b** led comparably to **50** while **51b** furnished the epimeric enone **53**. To increase the throughput of **50**, we ultimately took advantage of the ease of its chromatographic separation from **53** and effected no intermediate purification during the several steps that intervene between **42** and these enones.

With a viable route to the structural framework of africanol secure, completion of the synthesis required proper installation of the angular hydroxyl and setting of methyl stereochemistry. The simplest means uncovered for effecting these transformations began with low-temperature diisobutylaluminum hydride reduction of **50**. A 95:5 mixture of allylic alcohols was obtained, the major constituent of which was assigned as **54** for reasons of steric approach control (Scheme XI). This conclusion was confirmed by eventual elaboration of the natural product. The pure α alcohol **54**, after conversion to its *tert*-butyldimethylsilyl ether, was submitted to peracid oxidation and desilylation with tetra-*n*-butylammonium fluoride. Epoxide formation happened to be quite slow, and its stereochemical outcome sensitive to solvent. For example, the customarily small change from chloroform to dichloromethane resulted here in a product distribution crossover at 0 °C from 60:40 in favor of **57** to 40:60. The α surface of the double bond is clearly not as encumbered as one might initially surmise.

Nevertheless, the availability of both **57** and **58** allowed us to proceed separately to both africanol and its stereoisomer **61**. To achieve simultaneous removal of the hydroxyl group and cleavage of the oxirane ring, **57** was exposed to sulfene, and the resulting mesylate was reduced with lithium in liquid ammonia.[46] With access to **59** in this manner, subsequent hydrogenation proceeded with 100% stereoselectivity from the β face to give africanol (**1**). ^{1}H NMR (300-MHz) spectra of the synthetic sample and the natural product were superimposable.[47]

When **58** was treated analogously, the isomeric saturated tricyclic alcohol **61** was obtained. The α orientation of its secondary methyl group has been established by selected NOE experiments at 500 MHz. Most revealing was the effect of double irradiation of the hydroxyl proton singlet, which gave rise to a 4% enhancement of the integral associated with the methyl doublet at δ 0.76. Africanol (**1**) does not display a comparable proximity effect.

An alternative, more abbreviated route from **54** to **59** deserves brief comment despite its inapplicability. As shown in Scheme XI, reaction of **54** with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine[48] occurred smoothly with inversion of configuration to yield the β-selenide **56**. Although allylic selenoxides are known[49] to undergo ready [2,3]sigmatropic shift, the oxidized form of **56** failed to undergo reaction, presumably because of a kinetic preference for cyclopentadiene ring formation. In this connection, we have subsequently come to realize that this contrathermodynamic isomerization of allylic alcohols has been applied successfully only to acyclic and six-membered cyclic systems.[50] Perhaps our present experience with a cyclopentenyl derivative (i.e., eventual polymer formation) will prove equally problematic in other structurally related contexts.

Summary. The total syntheses of dactylol and africanol have been achieved from bicyclo[5.1.0]octane precursors by routes that for the most part are stereocontrolled. A pair of X-ray analyses were completed during this venture, thereby confirming the structural assignments to **15b** and **24**. Two ortho ester Claisen rearrangements were observed to proceed with superb transfer of chirality. Although the latter events were anticipated, other transformations owing their stereoselectivity to the conformational rigidity of the bicyclo[5.1.0]octane scaffolding are perhaps less obvious.

(46) (a) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312. (b) Marshall, J. A.; Jenson, T. M. *J. Org. Chem.* **1984**, *49*, 1707.

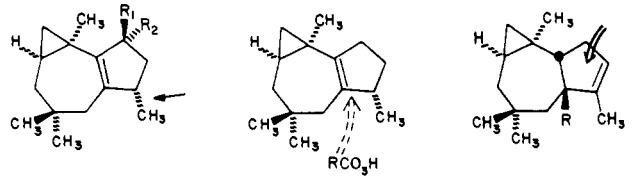
(47) We thank Dr. J. C. Braekman of the Universite Libre de Bruxelles for providing us with a generous sample of africanol.

(48) (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. (b) Sevrin, M.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1980**, 656.

(49) (a) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Menchem, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, *34*, 1049. (b) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981.

(50) (a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (b) Reich, H. J. *Organic Chemistry: Oxidation in Organic Chemistry*; Trahanovksy, W. S., Ed.; Academic Press: New York, 1978; Vol. 5-C, p 1.

For example, the findings that **17** is the dominant stereoisomer to arise from $RhCl_3$-promoted isomerization of **17–19** and that **25** is the major dithioketal resulting from acid-catalyzed condensation with ethanedithiol suggest that the secondary methyl group is thermodynamically more stable when in the α orientation. In a related context, the stereochemical course of the epoxidation of **27** indicates the α surface to be more accessible to the peracid reagent (see K). This tendency is lessened when the double bond is exocyclic to the seven-membered ring as in **54**.



J K L

Catalytic hydrogenation of two tricyclic intermediates (**19** and **59**) having their sites of unsaturation as in L is β selective. In contrast, the lesser substituted double bond in **32** is reduced preferentially from the α surface. Also noteworthy is the outcome of the Dibal reductions of **17** and **50**, both of which exhibit a high preference for β attack and formation of the α alcohols. These considerations should prove useful for synthesis of other members of the evergrowing africane class of sesquiterpenes.

Experimental Section

2,5,5-Trimethyl-2-cyclohepten-1-one (12). To a stirred solution of triethylamine (48.48 g, 0.48 mol) in dry dimethylformamide (80 mL, both components were freshly distilled from calcium hydride) was added 26.08 g (0.24 mol) of chlorotrimethylsilane (distilled before use) and 25.2 g (0.20 mol) of 4,4-dimethylcyclohexanone (**11**). This mixture was heated at the reflux temperature for 6 h, cooled to room temperature, and diluted with 300 mL of pentane. The precipitated triethylamine hydrochloride was separated by filtration and washed well with pentane (3 × 100 mL). The combined filtrates were washed with ice-cold saturated sodium bicarbonate solution (3 × 300 mL) and brine (50 mL) prior to drying. Solvent evaporation left 34.12 g (86%) of the silyl enol ether that was used directly without further purification.

n-Butyllithium in hexane (201.3 mL of 1.55 M, 0.372 mol) was slowly added under nitrogen during 6 h to a cold (−40 °C), magnetically stirred solution of the preceding product (27.02 g, 0.130 mol) and 1,1-dichloroethane (41.2 g, 0.416 mol) in anhydrous ether (50 mL). The mixture was allowed to warm to 0 °C over 1 h, at which point it was diluted with ether (100 mL), washed with water (4 × 50 mL), dried, and concentrated. The residual oil (25.5 g) was dissolved in a mixture of toluene (500 mL) and ethylene glycol (45 mL) and heated at the reflux temperature under nitrogen for 24 h. The toluene was removed to leave **12** dissolved in ethylene glycol. Characterization of the enone was achieved by subjecting a small aliquot to chromatography on silica gel followed by preparative VPC (6 ft × 0.25 in 5% SE-30, 92 °C): IR (neat, cm^{-1}) 1669; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44–6.38 (m, 1 H), 2.44–2.40 (m, 2 H), 2.07 (dd, J = 7.5, 0.87 Hz, 2 H), 1.79 (dd, J = 2.1, 0.87 Hz, 3 H), 1.49–1.45 (m, 2 H), 0.95 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 205.61, 139.15, 138.95, 39.66, 39.57, 34.48, 33.23, 29.61 (2 C), 18.69; MS, m/z (M^+) calcd 152.1201, obsd 152.1205.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.51; H, 10.96.

***cis*-1,5,5-Trimethylbicyclo[5.1.0]octan-2-one (13).** The bulk of the material was taken up in benzene (500 mL), treated with *p*-toluenesulfonic acid (550 mg), and heated at reflux for 48 h with azeotropic removal of water (Dean–Stark trap). The cooled mixture was washed with saturated sodium bicarbonate solution (50 mL) and water (2 × 50 mL) before drying. Solvent evaporation was followed by vacuum distillation to afford 21.0 g (82.5% overall) of the ketal, bp 63–66 °C/1.3 torr: IR (neat, cm^{-1}) 3080, 1260, 1070, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (dt, J = 7, 1.3 Hz, 1 H), 3.95 (s, 4 H), 1.98 (d, J = 7.1 Hz, 2 H), 1.80–1.76 (m, 2 H), 1.71 (s, 3 H), 1.51–1.47 (m, 2 H), 0.89 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.62, 126.26, 111.11, 64.69 (2 C), 38.99, 36.52, 32.56, 32.01, 29.40 (2 C), 20.05; MS, m/z (M^+) calcd 196.1463, obsd 196.1467.

A solution of ethylzinc iodide in ether (12 mL of 1 M, 0.012 mol) was introduced via syringe into a flame-dried, 250-mL, three-necked flask. Following the addition of diiodomethane (0.76 g, 2.8 mmol), the reaction mixture was magnetically stirred under nitrogen at room temperature for 1.5 h. The above ketal (500 mg, 2.55 mmol) was next introduced, and heating at the reflux temperature was maintained for 25 h. The solution was carefully poured into 1 M hydrochloric acid (20 mL), and the layers were separated. The aqueous phase was extracted with ether (2 × 25 mL), and the combined organic layers were washed with sodium thiosulfate solution (1 M, 2 × 25 mL) and water (25 mL). Drying and solvent evaporation left 493 mg (92%) of the cyclopropanated ketal as a colorless oil which was directly hydrolyzed; IR (neat, cm^{-1}) 2950, 1455, 1360; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93–3.82 (m, 4 H), 2.25 (dt, J = 4.7, 2.7 Hz, 1 H), 1.71 (ddd, J = 14, 6.1, 1.5 Hz, 1 H), 1.57–1.46 (m, 2 H), 1.28–1.18 (m, 2 H), 1.11 (s, 3 H), 0.97 (s, 3 H), 0.87 (s, 3 H), 0.62–0.45 (m, 2 H), 0.41 (dd, J = 8.4, 3.4 Hz, 1 H); MS, m/z (M^+) calcd 210.1620, obsd 210.1624.

The ketal (215 mg, 1.0 mmol) was dissolved in acetone (10 mL) containing 2 drops of 1 N sulfuric acid and stirred at room temperature for 8 h. The reaction mixture was poured into saturated sodium bicarbonate solution (50 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with water (50 mL), dried, and concentrated to give 170 mg (100%) of **13** as a colorless oil: IR (neat, cm^{-1}) 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 2.74–2.65 (m, 1 H), 2.23 (ddd, J = 15, 10, 3.5 Hz, 1 H), 1.89 (dd, J = 15, 4.9 Hz, 1 H), 1.73 (ddd, J = 13.9, 10.2, 3.8 Hz, 1 H), 1.33–1.29 (m, 1 H), 1.29 (s, 3 H), 1.00 (s, 3 H), 0.89–0.83 (m, 1 H), 0.86 (s, 3 H), 0.74–0.55 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.44, 42.97, 37.66, 37.21, 33.13, 31.76, 30.59, 26.60, 20.65, 19.76, 19.03; MS, m/z (M^+) calcd 166.1358, obsd 166.1361.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.17; H, 11.01.

(1*R,7*S**)-3-[(*E*)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octan-2-one (14).** Cold (0 °C), dry tetrahydrofuran (1 L) was treated sequentially with *n*-butyllithium (112.7 mL of 1.55 M, 0.17 mol) and isopropylcyclohexylamine (28.6 mL, 0.17 mol) under a nitrogen atmosphere. After 15 min, the solution was cooled to −78 °C, and 23.32 g (0.14 mol) of **13** dissolved in anhydrous ether (50 mL) was introduced by syringe. The enolate was allowed to form during 1.5 h, whereupon acetaldehyde (13.4 mL, ca. 2 equiv, dried over K_2CO_3 at −78 °C for 15 min) was added dropwise from a syringe. The reaction mixture was stirred for 30 min and immediately neutralized with 1 equiv of acetic acid in ether (50 mL). The mixture was poured into saturated ammonium chloride solution, and the organic phase was separated. The aqueous layer was extracted with ether (500 mL), and the combined organic solutions were washed with saturated sodium bicarbonate solution and brine, dried, and evaporated. There was obtained 22.50 g (76.5%) of aldol product as a colorless oil that was immediately acetylated: IR (CCl_4, cm^{-1}) 3500, 3080, 1674; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (dt, J = 6.1, 6.0 Hz, 1 H), 3.34 (br, 1 H), 2.16 (ddd, J = 12, 9.8, 6.0 Hz, 1 H), 1.97 (dd, J = 14, 7.5 Hz, 1 H), 1.46 (dd, J = 13.4, 12.4 Hz, 1 H), 1.30–1.02 (m, 5 H), 1.19 (s, 3 H), 1.15 (d, J = 6.3 Hz, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.40, 69.25, 50.92, 40.34, 39.60, 33.50, 33.40, 32.0, 28.1, 24.1, 23.51, 21.0, 18.9; MS, m/z (M^+) calcd 210.1620, obsd 210.1615.

A solution of the aldol (21.50 g, 0.102 mol), acetic anhydride (19.8 mL, 2 equiv), triethylamine (30.34 mL, 1.3 equiv), and 4-(dimethylamino)pyridine (113 mg) in dichloromethane (500 mL) was heated at the reflux temperature for 6 h. The cooled reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried, and evaporated to furnish the acetoxy ketone as a colorless liquid (24.8 g, 96.1%): IR (neat, cm^{-1}) 1740, 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (dt, J = 6.1, 6.0 Hz, 1 H), 2.43 (ddd, J = 9.6, 6.1, 3.1 Hz, 1 H), 1.99 (s, 3 H), 1.92 (dd, J = 15, 5.7 Hz, 1 H), 1.64 (dd, J = 12.9, 13.1 Hz, 1 H), 1.33 (dd, J = 13.8, 3.3 Hz, 1 H), 1.24 (s, 3 H), 1.20 (d, J = 6.3 Hz, 3 H), 1.06–0.79 (m, 3 H), 0.98 (s, 3 H), 0.89 (s, 3 H); MS, m/z (M^+–HOAc) calcd 192.1514, obsd 192.1533.

A solution of the acetoxy ketone (24.8 g, 98.4 mmol) and DBU (29.4 mL, 2 equiv) in 450 mL of benzene was heated to reflux for 6 h, cooled, washed with water, and dried. Evaporation gave 17.64 g (93.2%) of **14** as a colorless liquid: IR (neat, cm^{-1}) 1690, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (q, J = 7.4 Hz, 1 H), 2.41, 2.32 (ABq, J = 13.8 Hz, 2 H), 1.82–1.75 (m, 1 H), 1.79 (d, J = 7.4 Hz, 3 H), 1.27 (s, 3 H), 1.13 (s, 3 H), 0.97–0.87 (m, 1 H), 0.81 (s, 3 H), 0.67 (dd, J = 4.9, 6.8 Hz, 1 H), 0.43–0.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.66, 137.14, 136.59, 42.50, 37.92, 35.86, 28.69, 28.59, 27.22, 21.24, 19.40, 17.76, 14.47; MS, m/z (M^+) calcd 192.1518, obsd 192.1514.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.13; H, 10.50.

(1*R,2*S**,7*S**)-3-[(*E*)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octan-2-ol (15a).** A solution of **14** (585 mg, 3.04 mmol) and cerium trichloride (824 mg, 10% excess) in methanol (3 mL) was stirred for 15 min and sodium borohydride (0.23 g, 6.05 mmol) was added carefully in small portions. With protection from atmospheric moisture, the reaction

mixture was stirred at room temperature for 2 h before being poured into 1 N sodium hydroxide solution (50 mL). After 15 min of stirring, the mixture was filtered through Celite, and the filter cake was washed with ether (50 mL). The layers in the filtrate were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic solutions were washed with ether (3 × 30 mL). The combined organic solutions were washed with water (50 mL), dried, and concentrated to give 581 mg (97%) of **15a** as a clear oil. An analytical sample was obtained by preparative VPC (2 ft × 0.25 in 5% SE-30, 110 °C); IR (neat, cm^{-1}) 3410; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (q, J = 6.8 Hz, 1 H), 4.18 (s, 1 H), 2.15 (dd, J = 13.2, 2.3 Hz, 1 H), 1.96 (d, J = 13.2 Hz, 1 H), 1.78–1.70 (m, 1 H), 1.64 (dd, J = 6.1, 1.1 Hz, 3 H), 1.38 (s, 1 H), 1.31 (dd, J = 15, 10.4 Hz, 1 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.90 (s, 3 H), 0.69 (t, J = 4.5 Hz, 1 H), 0.60–0.50 (m, 1 H), 0.46 (dd, J = 8.4, 3.8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.14. Found: C, 80.60; H, 11.40.

The *p*-nitrobenzoate **15b**, prepared in the usual way, was obtained as pale yellow crystals, mp 125–126 °C (from hexane). An X-ray analysis was carried out on this material.

(*βR*,1R*,7S)-β,1,5,5-Tetramethylbicyclo[5.1.0]oct-2-ene-3-propionic Acid (16).** A solution of **15a** (37 mg, 0.19 mmol) and triethyl orthoacetate (310 mg, 1.91 mmol) in xylene (0.5 mL) containing a trace of propionic acid was heated at the reflux temperature under nitrogen for 3 h. The cooled reaction mixture was diluted with ether (10 mL) and washed successively with 10% hydrochloric acid (10 mL), saturated sodium bicarbonate solution (2 × 10 mL), and saturated brine (10 mL). Following drying and solvent evaporation, there was isolated 39 mg of pale yellow oil. Purification by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) gave the ethyl ester as a colorless oil (35.5 mg, 72%); IR (neat, cm^{-1}) 3060, 1735; ^1H NMR (200 MHz, $CDCl_3$) δ 5.33 (s, 1 H), 4.09 (q, J = 7 Hz, 2 H), 2.50–2.35 (m, 3 H), 2.08 (dd, J = 15.7, 8.6 Hz, 1 H), 1.8–1.5 (m, 3 H), 1.23 (t, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H), 0.80 (s, 3 H), 0.67–0.61 (m, 1 H), 0.38 (dd, J = 7.3, 3.9 Hz, 1 H), 0.05 (t, J = 4 Hz, 1 H); MS, m/z (M^+) 264.2089, obsd 264.2128.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.69. Found: C, 77.21; H, 10.60.

The ester (117 mg, 0.442 mmol) was added to 10 equiv of potassium hydroxide in methanol (30 mL), and this mixture was heated at the reflux temperature for 5 h. Following reaction with dichloromethane (30 mL), the separated aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 × 30 mL). The combined extracts were washed with brine, dried, and concentrated to furnish 89 mg (85%) of pure **16**. Crystallization from ether gave colorless crystals, mp 44–45.5 °C; IR (CCl_4, cm^{-1}) 3600–3000, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (s, 1 H), 2.54–2.45 (m, 3 H), 2.15 (dd, J = 6.0, 5.7 Hz, 1 H), 1.72 (dd, J = 12.6, 3.2 Hz, 1 H), 1.56 (d, J = 13.3 Hz, 1 H), 1.09 (d, J = 6.7 Hz, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.84 (s, 3 H), 0.78–0.62 (m, 2 H), 0.42 (dd, J = 7.4, 3.8 Hz, 1 H), 0.05 (t, J = 4.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.44, 142.01, 126.23, 43.71, 42.31, 41.56, 37.59, 30.93, 30.72, 29.83, 24.32, 20.10, 19.14, 18.93, 18.53; MS, m/z (M^+) calcd 236.1776, obsd 236.1858.

Friedel–Crafts Cyclization of 16. A. Aluminum Chloride Method. Acid **16** (157 mg, 0.665 mmol) was dissolved in dry benzene (60 mL). The solution was cooled in ice, and oxalyl chloride (0.68 mL) was added with swirling. The mixture was stirred at 0 °C for 30 min and allowed to stand at room temperature for 1.5 h. Volatiles were removed at 40–45 °C and 30 torr. Benzene (10 mL) was added, and the solution was evaporated. Following repetition of this treatment, the acid chloride was taken up in carbon disulfide (3 mL), and 0.35 g of anhydrous aluminum chloride was introduced with rapid swirling. The flask was flushed with dry nitrogen, sealed, and shaken for 20 h. Hydrolysis was accomplished by slow addition of 1 mL of acetic acid and subsequent careful dilution with 10 mL of water. The product was taken up into pentane (3 × 25 mL), and the combined organic layers were washed with water and dried. The dark-colored solution was evaporated, diluted with ether, filtered through Celite, and again concentrated. Purification of the major component by preparative TLC on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 50 mg (34%) of **19** as a colorless liquid: IR (CCl_4, cm^{-1}) 1710, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, J = 1.7, 1.2 Hz, 1 H), 2.89 (d, J = 12 Hz, 1 H), 2.05 (s, 3 H), 1.96–1.85 (m, 2 H), 1.86, 1.06 (ABq, J = 13.6 Hz, 2 H), 1.10 (s, 3 H), 1.12–0.99 (m, 1 H), 0.95 (s, 6 H), 0.83–0.77 (m, 1 H), 0.52–0.45 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.2, 178.4, 131.0, 60.9, 46.4, 45.1, 44.1, 34.1, 34.1, 33.6, 24.2, 23.7, 19.8, 19.2, 18.1, 16.9; MS m/z (M^+) calcd 218.1670, obsd 218.1664.

B. Stannic Chloride Method. A 405-mg (1.716 mmol) sample of **16** was transformed into the acid chloride in the predescribed manner and dissolved in 120 mL of 1,2-dichloroethane. This solution was cooled to 0 °C under nitrogen and stirred rapidly while 0.312 mL of stannic chloride was introduced. After 25 min, the reaction mixture was washed with saturated sodium bicarbonate solution, diluted with 50 mL of dichloromethane, and rapidly filtered through a short silica gel column before concentration. The resulting oil (360 mg, 96%) was found by VPC analysis (6 ft × 0.25 in. OV-11, 160 °C) to consist of a mixture of **17**, **18**, and **19** in a ratio of 12:24:64. The three components were subsequently isolated preparatively.

For **17**: colorless oil; IR (neat, cm^{-1}) 1705, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 2.69–2.54 (m, 3 H), 2.09 (d, J = 13.6 H, 1 H), 1.98 (dd, J = 16.8, 1.0 Hz, 1 H), 1.83 (dd, J = 12, 3.8 Hz, 1 H), 1.16 (d, J = 8.2 Hz, 3 H), 1.14 (s, 3 H), 1.13 (s, 3 H), 0.86 (s, 3 H), 0.83–0.73 (m, 2 H), 0.54–0.49 (m, 1 H), 0.27 (s, 1 H); MS, m/z (M^+) calcd 218.1670, obsd 218.1664.

For **18**: colorless oil; IR (neat, cm^{-1}) 1705, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71–2.62 (m, 1 H), 2.64 (dd, J = 18.1, 16 Hz, 1 H), 2.62, 2.13 (ABq, J = 14.7 Hz, 2 H), 1.95 (dd, J = 18, 16 Hz, 1 H), 1.84 (dd, J = 13.5, 3.6 Hz, 1 H), 1.17 (s, 3 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.13 (s, 3 H), 0.94 (s, 3 H), 0.87–0.28 (m, 3 H); MS, m/z (M^+) calcd 218.1670, obsd 218.1676.

Ketone **19** exhibited spectral data identical with the material isolated in Part A.

Anal. (for **17–19**) Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.15; H, 10.51.

Rhodium Trichloride-Promoted Isomerization of 17–19. A 360-mg sample of the enone mixture and 16.7 mg of rhodium trichloride trihydrate in absolute ethanol (3 mL) was placed in a sealed tube and heated at 100 °C for 24 h. The solvent was evaporated, and the residue was partitioned between dichloromethane (300 mL) and water (20 mL). The organic layer was dried and concentrated, and the residual oil was purified by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). The colorless oil (210 mg, 58%) was determined by VPC analysis to consist of **17** (68%), **18** (29%), and **19** (3%).

(1a*R,4a*R**,5*R**,7a*S**,7b*S**)-Decahydro-3,3,5,7b-tetramethyl-7*H*-cycloprop[*e*]azulen-7-one (20).** A solution of **19** (16.6 mg) in ethyl acetate (2 mL) containing 3.8 mg of platinum oxide was hydrogenated at 40 psi in a Parr apparatus for 24 h. The catalyst was separated by filtration, and the filtrate was concentrated to give 15 mg of **20**: IR (neat, cm^{-1}) 3090, 1750; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47–1.60 (series of m, 9 H), 1.12 (d, J = 6.3 Hz, 3 H), 1.04 (s, 3 H), 0.93 (s, 3 H), 0.91 (s, 3 H), 0.85–0.41 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 190.45, 62.17, 49.36, 48.32, 44.42, 43.90, 35.97, 33.69, 29.66, 24.20, 23.55, 20.10, 19.91, 19.00, 18.09; MS, m/z (M^+) calcd 220.1827, obsd 220.1823.

(γ*R,1*R**,7*S**)-γ,1,5,5-Tetramethylbicyclo[5.1.0]oct-2-ene-3-propanol (21).** A mixture of **16** (25 mg) and lithium aluminum hydride (12 mg) in dry ether (5 mL) was stirred for 10 h. The mixture was cooled in ice, and excess hydride was carefully decomposed with ethanol (1 mL) and water (2 mL). The product was extracted into ether (3 × 25 mL), and the combined solutions were dried and evaporated to give 20.7 mg (88%) of **21** as a colorless oil: IR (neat, cm^{-1}) 3500–3300, 3040, 3000–2880; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1 H), 3.61 (octet, J = 6.9 Hz, 2 H), 2.46 (d, J = 13 Hz, 1 H), 2.12 (sextet, J = 6.8 Hz, 1 H), 1.71–1.51 (m, 4 H), 1.47 (br s, 1 H), 1.01 (s, 3 H), 1.00 (d, J = 7 Hz, 3 H), 0.99 (s, 3 H), 0.79 (s, 3 H), 0.72–0.41 (m, 2 H), 0.39 (dd, J = 5.6, 3.8 Hz, 1 H), 0.02 (t, J = 3.7 Hz, 1 H); MS, m/z (M^+) calcd 222.1984, obsd 222.1988.

(*βR*,1R*,7S)-β,1,5,5-Tetramethylbicyclo[5.1.0]oct-2-ene-3-propionaldehyde (22).** Chromium trioxide (150 mg) was slowly added to 1.5 mL of pyridine at such a rate that the temperature was kept below 30 °C. The resulting yellow solid was washed with hexane (3.2 mL) and quickly dissolved in dichloromethane (3 mL). Alcohol **21** (50 mg) was slowly introduced with stirring, and after 10 min the supernatant was decanted from the gummy black deposit. The solution was washed with water and 1 N hydrochloric acid prior to drying. The solvent was evaporated, and the residual oil was purified by preparative TLC on silica gel. There was isolated 30.2 mg (61%) of **22** as a colorless oil: IR (neat, cm^{-1}) 3055, 2700, 1725, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (m, 1 H), 5.34 (s, 1 H), 2.52–2.42 (m, 2 H), 2.45, 1.49 (ABq, J = 13 Hz, 2 H), 2.27–2.18 (m, 1 H), 1.68 (dd, J = 13, 3.7 Hz, 1 H), 1.49 (d, J = 13 Hz, 1 H), 1.01 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.79 (s, 3 H), 0.71–0.55 (m, 2 H), 0.38 (dd, J = 7.6, 3.9 Hz, 1 H), 0.00 (t, J = 3.9 Hz, 1 H); MS, m/z (M^+) calcd 220.1857, obsd 220.1814.

(1a*R,4a*R**,5*R**,7*S**,7a*S**,7b*S**)-4a,7a-Epoxydecahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulen-7-ol (24).** A cold (0 °C), magnetically stirred solution of enones **17–19** (85 mg, 0.390 mmol) in anhydrous ether (10 mL) was treated with diisobutylaluminum hydride (0.8 mL of 1 M in hexane) and stirred at 0 °C for 5 h. The reaction mixture was allowed to warm to room temperature, washed with saturated ammonium chloride solution, dried, and concentrated. The resulting alcohols (85 mg, 100%) were dissolved in dry benzene (10 mL), cooled to 5 °C, and

treated with *m*-chloroperbenzoic acid (75.2 mg, 10% excess). After 4 h of stirring at 0 °C, the mixture was set aside overnight at room temperature. Solid calcium hydroxide was added, and the mixture was stirred for 10 min. Filtration and evaporation of the solvent gave a mixture which was separated by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether). The major constituent was isolated as a colorless crystalline solid, mp 88–91 °C, and identified as **24** by X-ray crystallography: IR (KBr, cm^{-1}) 3500–3300, 3062, 2950, 1455, 1390, 1200, 1050, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 5.7 Hz, 1 H), 2.03–1.21 (series of m, 4 H), 1.89, 1.47 (ABq, J = 14.3 Hz, 2 H), 1.18 (s, 3 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.95–0.53 (series of m, 4 H), 0.41 (t, J = 3.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 75.08, 71.36, 70.76, 43.59, 40.20, 37.41, 35.28, 31.89, 30.96, 29.37, 22.92, 20.46, 18.99, 17.18, 13.46; MS, m/z (M^+) calcd 236.1759, obsd 236.1761.

Dithioketalization of 17–19. A mixture of the three enones (105 mg, 0.482 mmol, ratio 12:24:64), 1,2-ethanedithiol (0.5 mL), *p*-toluenesulfonic acid monohydrate (10 mg), and benzene (10 mL), was heated at reflux under a Dean-Stark trap for 13 h. The cooled reaction mixture was diluted with ether, washed several times with 1 N sodium hydroxide solution, dried, and freed of solvent. The desired products were separated from unreacted starting material (31 mg) by MPLC on silica gel (elution with petroleum ether). There was isolated 74 mg (74%) of an 83:17 mixture of **25** and **26** (capillary VPC analysis): IR (neat, cm^{-1}) 3070, 2750, 1745, 1457, 1370, 1360, 1275; ^1H NMR (300 MHz, $CDCl_3$) δ 3.47–3.17 (m, 4 H), 2.77–2.56 (m, 1 H), 2.68, 1.75 (ABq, J = 12.7 Hz, 2 H), 2.25 (d, J = 13.1 Hz, 1 H), 2.08–1.97 (m 1 H), 1.69–1.62 (m, 1 H), 1.26 (s, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.01 (s, 3 H), 0.77 (s, 3 H), 0.68–0.46 (m, 4 H); MS, m/z (M^+) calcd 294.1476, obsd 294.1474.

Raney Nickel Desulfurization of 25 and 26. An 83:17 mixture of **25** and **26** (87 mg, 0.296 mmol), W-2 Raney nickel (3 g), and absolute ethanol (0.5 mL) was stirred at 25 °C for 10 min. The nickel was removed by filtration and rinsed with ethanol. The combined filtrates were evaporated, and the hydrocarbon mixture was separated by chromatography on silica gel impregnated with 2.2% silver nitrate. These conditions gave 40 mg (66%) of **27** and **28** (83:17): IR (neat, cm^{-1}) 3060, 2800, 2680, 1460, 1380–1370, 1200; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48–1.99 (m, 5 H), 1.76–1.56 (m, 2 H), 1.37–1.22 (m, 2 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.78 (s, 3 H), 0.76–0.59 (m, 1 H), 0.42 (dd, J = 3.9, 2.8 Hz, 1 H), 0.019 (t, J = 4.1 Hz, 1 H); MS, m/z (M^+–1) calcd 203.1800, obsd 203.1807.

(1a*R,4a*R**,5*R**,7a*R**,7b*S**)-4a,7a-Epoxydecahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulene (29).** An unpurified mixture of hydrocarbons **27** and **28** (17 mg) dissolved in 0.5 mL of dry dichloromethane was treated with *m*-chloroperbenzoic acid (43.7 mg, 3 equiv) at room temperature. The reaction mixture was stirred for 10 min and washed with saturated sodium bicarbonate solution. The organic layer was dried and concentrated. The residual oil was separated into its two components by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether). There was isolated 8 mg (44%) of **29** and 1.7 mg (11%) of its epimer.

For **29**: IR (neat, cm^{-1}) 2790, 1450, 1375, 1362, 1190, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06–1.92 (m, 1 H), 1.89–1.79 (m, 1 H), 1.83 (d, J = 15 Hz, 1 H), 1.58 (d, J = 15 Hz, 1 H), 1.57–1.40 (m, 1 H), 1.25–1.19 (m, 1 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.98–0.85 (m, 3 H), 0.92 (s, 3 H), 0.70–0.56 (m, 2 H), 0.26 (t, J = 4.2 HZ, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 71.69 (2C), 45.75, 41.06, 37.89, 31.85, 31.56, 29.39, 28.57, 28.15, 22.37, 21.09, 19.57, 18.90, 13.78; MS, m/z (M^+) calcd 220.1827, obsd 220.1835.

(1a*R,4a*R**,5*R**,7a*R**,7b*S**)-4a,7a-Epoxydecahydro-3,3,5,7b-tetramethyl-7*H*-cycloprop[*e*]azulen-7-one (30).** A solution of **24** (190 mg, 0.804 mmol) in dichloromethane (5 mL) was added via syringe to a magnetically stirred suspension of pyridinium chlorochromate (0.35 g, 2 equiv) in the same solvent (10 mL). After 6 h, 20 mL of dry ether was added, and the supernatant was decanted from the black gum. The insoluble residue was rinsed thoroughly with ether (3 × 10 mL), and the combined organic solutions were concentrated. The residue was purified by MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) to give 122.4 mg (65%) of **30** as a colorless oil: IR (neat, cm^{-1}) 3078, 2778, 1740, 1360, 1210, 1000, 865; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21–1.80 (m, 4 H), 2.12 (d, J = 14.7 Hz, 1 H), 1.69 (d, J = 15 Hz, 1 H), 1.12 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.88–0.82 (m, 1 H), 0.64–0.57 (m, 2 H), 0.50–0.47 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.85, 69.57, 65.33, 43.77, 40.89, 40.38, 32.97, 31.63, 29.71, 28.63, 21.85, 19.81, 19.24, 13.93, 13.68; MS, m/z (M^+) calcd 234.1620, obsd 234.1607.

***cis*-1a,2,3,4,6,7b-Hexahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulene (32).** A magnetically stirred solution of **36** (250 mg, 1.14 mmol) in cold (−50 °C) tetrahydrofuran (8 mL) was treated with triethylamine (0.4 mL, 2.5 equiv) and thionyl chloride (90 μL, 1.1 equiv). After 30 min, the reaction mixture was allowed to warm to −20 °C and stirred for an additional 2 h at −20 to −10 °C. Ether (20 mL) was added, and the mixture was shaken with sodium bicarbonate solution and brine. Following drying and evaporation of the organic phase, the resulting oil was quickly subjected to flash chromatography on silica gel (elution with petroleum ether). There was obtained 140 mg (60%) of **32** as a sensitive colorless oil: IR (neat, cm^{-1}) 3078, 3009, 2960, 2935, 2920, 2875, 1650, 1590, 1480–1450, 1380, 1360; ^{1}NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 2.84 (t, J = 1.7 Hz, 2 H), 2.25–0.07 (series of m, 7 H), 1.92 (s, 3 H), 1.18 (s, 3 H), 1.10 (s, 3 H), 0.74 (s, 3 H); MS, m/z (M^+) calcd 202.1721, obsd 202.1725.

(1a*R,7b*S**)-Decahydro-3,3,5,7b-tetramethyl-4a*H*-cycloprop[*e*]azulene-4a,5-diol 4a-*m*-Chlorobenzoate (33a).** Buffer-washed *m*-chlorobenzoic acid (75.2 mg, 1.1 equiv) in dichloromethane (3 mL) was added dropwise to a cold (−40 °C), magnetically stirred solution of **32** (80 mg, 0.40 mmol) in dichloromethane (7 mL) containing sodium bicarbonate (109.3 mg, 1.5 equiv). The reaction mixture was stirred at −40 °C for 3 h, at −5 to −10 °C for 2 days, and at 10 °C for 12 h. Solid calcium hydroxide was added, and the mixture was stirred for 10 min. Filtration and solvent evaporation gave a residue that was subjected to MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). One stereoisomer of **33a** was isolated in pure condition (128 mg, 90%): IR (neat, cm^{-1}) 3450, 3065, 2930, 2880, 1720, 1575, 1460, 1426, 1365, 1350, 1285, 1250, 1120, 1085, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.35 (m, 4 H), 5.69 (m, 1 H), 2.58 (dd, J = 14.7, 7.2 Hz, 1 H), 2.45 (dd, J = 14.4, 1.8 Hz, 1 H), 2.08–2.00 (m, 2 H), 1.81–1.72 (m, 2 H), 1.33 (s, 3 H), 1.19 (s, 3 H), 0.87 (s, 3 H), 0.85–0.66 (m, 1 H), 0.59–0.48 (m, 2 H), 0.18 (t, J = 4.8 Hz, 1 H); MS, m/z (M^+–H_2O) calcd 356.1543, obsd 356.1568.

(1a*R,7b*S**)-Decahydro-3,3,5,7b-tetramethyl-4a*H*-cycloprop[*e*]azulene-4a,5-diol 4a-Acetate (33b).** To a cold (−40 °C), magnetically stirred mixture of **32** (38 mg, 0.188 mmol), sodium bicarbonate (70 mg, 0.812 mmol), and dichloromethane (3 mL) was added 40% peracetic acid (43.2 μL, 0.18 mmol) dropwise. The reaction mixture was stirred at this temperature for 2 h and at 0 °C for 24 h. Water and dichloromethane were added, and the separated organic layer was dried and concentrated. By means of HPLC on silica gel, it proved possible to separate three products in 85% combined yield. In order of elution, these products were the double bond isomer of **33b** (11 mg), an unknown substance (11 mg), and **33b** (21 mg).

For **33b**: IR (neat, cm^{-1}) 3450–3300, 1730, 1240, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (m, 1 H), 2.47–2.36 (m, 2 H), 2.06 (s, 3 H), 1.99–1.64 (m, 4 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 0.84 (s, 3 H), 0.86–0.76 (m, 1 H), 0.57–0.49 (m, 2 H), 0.14–0.11 (m, 1 H); MS, m/z (M^+–CH_3CO_2) calcd 219.1749, obsd 219.1758.

Hydrogenation of 32. A solution of **32** (8 mg, 0.04 mmol) in ethyl acetate (1 mL) was shaken under 1.5 atmospheres of hydrogen at 0 °C with platinum oxide (2 mg) for 3 days. The mixture was filtered, and the filtrate evaporated to give a mixture of **34** and **7** in a ratio of 73:19 in addition to a small amount of an unknown substance (VPC analysis). Hydrocarbon **7**, also a natural product,[1] exhibits characteristic methyl shifts at δ 1.86, 0.91, 0.86, and 0.86, and these signals were clearly observed for the minor hydroazulenoid component of this hydrogenation mixture.

Singlet Oxygenation of 36. A solution of **36** (220 mg, 1.0 mmol) in 5 mL of dry pyridine containing 2 mg of *meso*-tetraphenylporphine was irradiated with a 450-W Hanovia lamp through Pyrex for 4 days as oxygen was continuously bubbled through. The reaction mixture was filtered through charcoal and evaporated under reduced pressure. The crude product was separated into its four components by MPLC on silica gel (elution with 9% ethyl acetate in petroleum ether).

For **37**: 15 mg (7.7%); IR (neat, cm^{-1}) 3090, 3050, 2940, 2900, 1705, 1425, 1385, 1370, 1230–1175, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72–1.57 (series of m, 6 H), 1.24 (s, 3 H), 1.14 (s, 3 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.91 (s, 3 H), 0.86 (m, 1 H), 0.68 (m, 2 H), 0.34 (t, J = 5.2 Hz, 1 H); MS, m/z (M^+) calcd 236.1611, obsd 236.1610.

For **38**: 24 mg (12%); IR (neat, cm^{-1}) 3400, 3090, 2850, 1780, 1690, 1635, 1385; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85–0.70 (series of m, 9 H), 1.21 (s, 3 H), 1.14 (s, 3 H), 0.99 (d, J = 6.4 Hz, 3 H), 0.89 (s, 3 H), 0.86 (m, 1 H), 0.51 (dd, J = 4.4, 2.4 Hz, 1 H), 0.13 (t, J = 4.4 Hz, 1 H); MS, m/z (M^+) calcd 236.1773, obsd 236.1803.

For **39**: 32 mg (16%); IR (neat, cm^{-1}) 3500, 3090, 3050, 2850, 1755, 1653, 1480, 1390, 1372, 1310, 1220; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, J = 1.3 Hz, 1 H), 2.2–0.8 (series of m, 6 H), 1.96 (d, J = 1.3 Hz, 3 H), 1.27 (s, 3 H), 1.20 (s, 3 H), 0.89 (s, 3 H), 0.89–0.84 (m, 1 H), 0.58 (dd, J = 4.4, 2.4 Hz, 1 H), 0.20 (t, J = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.50, 114.59, 114.30, 92.35, 51.91, 44.51, 42.65, 35.32, 34.50, 27.25, 26.18, 24.97, 21.72, 17.10, 13.32; MS, m/z (M^+) calcd 234.1620, obsd 234.1637.

For **17**/**18**: 40 mg (22%); spectra as described earlier.

Also isolated was 35 mg of unreacted **36**.

Methyl (1*R,3*S**,7*S**)-1,5,5-Trimethyl-2-oxobicyclo[5.1.0]octane-3-carboxylate (40).** Into a dry 250-mL, three-necked flask was placed 3.88 g of 50% sodium hydride oil dispersion. While under nitrogen, the solid was washed 3 times with dry toluene and 3 times with anhydrous tetrahydrofuran (solvent removed by syringe). A solution of dimethyl carbonate (6.46 mL) in dry tetrahydrofuran (10 mL) was added dropwise, and the stirred mixture was heated to the reflux temperature. At this point, approximately 10% of a solution containing 4.50 g (27.1 mmol) of **13** in 10 mL of tetrahydrofuran was slowly added. Following introduction of a previously washed slurry of potassium hydride (0.23 g) in 4 mL of the same solvent, the reaction mixture was again heated to reflux, and the remaining ketone solution was dripped in during 45 min. Heating was continued for 15 h. The flask was then cooled in ice while acetic acid (50 mL) and saturated brine (60 mL) were added, followed by ether (200 mL) and solid sodium bicarbonate (to completion of gas evolution). The layers were separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were washed with brine, dried, and evaporated. Distillation of the residue afforded 5.16 g (85%) of **40** as a colorless oil: IR (neat, cm^{-1}) 3070, 1760, 1718, 1640, 1610, 1440; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 3.70 (s, 3 H), 2.17 (ABq, J = 27, 8 Hz, 2 H), 1.72 (dd, J = 14, 4.4 Hz, 1 H), 1.22 (s, 3 H), 0.97 (s, 3 H), 0.79–0.75 (m, 1 H), 0.72 (s, 3 H), 0.65–0.49 (m, 2 H), 0.44 (t, J = 4.8 Hz, 1 H); MS, m/z (M^+) calcd 224.1413, obsd 224.1453.

Methyl *cis*-1,5,5-Trimethylbicyclo[5.1.0]oct-2-ene-3-carboxylate (41). A solution of sodium borohydride (2.29 g) in ethanol (200 mL) was added dropwise during 1 h to a cold (0 °C), magnetically stirred solution of **40** (4.5 g, 20.1 mmol) in the same solvent (100 mL). After 15 min, dilute acetic acid was introduced, and solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, and this solution was washed with water, dried, and concentrated. There was obtained 4.27 g (94%) of the hydroxy ester which was directly acetylated: IR (neat, cm^{-1}) 3650, 3070, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 1 H), 3.68 (s, 3 H), 2.94 (d, J = 2.9 Hz, 1 H), 2.90 (m, 1 H), 1.86–1.62 (m, 2 H), 1.39–1.27 (m, 2 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.89 (s, 3 H), 0.89–0.84 (m, 1 H), 0.65–0.54 (m, 1 H), 0.38 (dd, J = 8.6, 3.9 Hz, 1 H); MS, m/z (M^+) calcd 226.1569, obsd 226.1560.

A solution consisting of β-hydroxy ester (1.27 g, 5.62 mmol), acetic anhydride (1.085 mL, 2 equiv), triethylamine (1.665 mL, 1.3 equiv), 4-dimethylaminopyridine (62 mg), and dichloromethane (100 mL) was heated to the reflux temperature for 2 days. After cooling, 5% sodium acetate solution was added, and the separated organic phase was washed with saturated sodium bicarbonate solution and brine. Following drying and solvent evaporation, there was isolated 1.39 g (92%) of the acetoxy ester as a colorless liquid: IR (neat, cm^{-1}) 3075, 1755–1735; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 3.62 (s, 3 H), 2.94 (dd, J = 12.7, 2.8 Hz, 1 H), 2.03 (s, 3 H), 1.80–1.71 (m, 3 H), 1.51–1.46 (m, 1 H), 1.14 (s, 3 H), 1.21–1.10 (m, 1 H), 1.01 (s, 3 H), 0.91 (s, 3 H), 0.66–0.56 (m, 1 H), 0.44 (dd, J = 8.5, 4.5 Hz, 1 H), 0.31 (t, J = 4.8 Hz, 1 H); MS, m/z (M^+) calcd 268.1674, obsd 268.1677.

A solution of the β-acetoxy ester (1.52 g, 5.67 mmol) and DBU (1.69 g) in dry benzene (100 mL) was heated at the reflux temperature for 3 days. The cooled mixture was washed with water, dried, and evaporated to give 1.05 g (89%) of **41** as a colorless liquid: IR (neat, cm^{-1}) 3070, 1715, 1625; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1 H), 3.69 (s, 3 H), 2.34 (m, 2 H), 1.74 (dd, J = 14, 4.6 Hz, 2 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 0.80–0.75 (m, 1 H), 0.75 (s, 3 H), 0.56–0.52 (, 2 H), 0.15 (t, J = 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.65, 144.31, 131.21, 51.62, 43.38, 37.12, 30.41, 29.97, 29.46, 23.00, 20.19, 19.75, 19.23; MS, m/z (M^+) calcd 208.1464, obsd 208.1465.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.75.

Methyl *cis*-1,5,5-Trimethylbicyclo[5.1.0]oct-2-en-3-yl Ketone (42). A solution of **41** (1.04 g, 5 mmol) and potassium hydroxide (930 mg) in 95% ethanol (50 mL) was heated at the reflux temperature for 6 h, cooled, and evaporated. The solid was dissolved in water and extracted twice with ether. The aqueous phase was acidified with 10% hydrochloric acid, and the precipitated acid was extracted with ether, dried, and evaporated. There was obtained 910 mg (94%) of colorless solid: mp 107–109 °C; IR (CCl_4, cm^{-1}) 3200–2600, 1680, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 12.24 (s, 1 H), 7.01 (s, 1 H), 2.41–2.36 (m, 2 H), 1.78 (dd, J = 14, 4.5 Hz, 1 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 0.94–0.82 (m, 1 H), 0.80 (s, 3 H), 0.61–0.53 (m, 2 H), 0.21 (t, J = 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.70, 147.06, 130.83, 43.38, 36.74, 30.35, 30.03, 29.40, 22.88, 20.26, 19.94, 19.24; MS, m/z (M^+) calcd 194.1307, obsd 194.1316.

A cold (−78 °C), nitrogen-blanketed solution of the carboxylic acid (208 mg, 1.07 mmol) in anhydrous ether (10 mL) was treated slowly with methyllithium (1.49 mL of 1.55 M in ether, 2.34 mmol). After 15 min, the reaction mixture was warmed to 0 °C, stirred for 3 h, and carefully treated with water. The ether phase was separated, washed with water, dried, and evaporated. The residue was purified by MPLC on silica gel (elution with 6% ethyl acetate in petroleum ether) to give 146 mg (71%) of **42** as a colorless oil: IR (neat, cm^{-1}) 3075, 1665, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1 h), 2.54 (d, J = 12.9 Hz, 1 H), 2.28 (s, 3 H), 2.11 (d, J = 12.4 Hz, 1 H), 1.74 (dd, J = 14.4, 4.6 Hz, 1 H), 1.14 (s, 3 H), 1.03 (s, 3 H), 0.90–0.83 (m, 1 h), 0.68 (s, 3 H), 0.62–0.57 (m, 1 H), 0.53–0.48 (m, 1 H), 0.20–0.19 (t, J = 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.38, 144.95, 140.74, 43.51, 35.08, 30.29, 29.97, 29.46, 25.37, 23.00, 20.45, 20.19, 19.36; MS, m/z (M^+) calcd 192.1514, obsd 195.1514.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.19; H, 10.49. Found: C, 80.78; H, 10.52.

Sodium Borohydride–Cerium Trichloride Reduction of 42. A solution containing **42** (700 mg, 3.65 mmol) and cerium trichloride (0.99 g, 10% excess) in methanol (25 mL) was stirred for 15 min before 280 mg of sodium borohydride was carefully introduced in small portions. The reaction mixture was stirred for 2 h, poured into 1 N sodium hydroxide solution (50 mL), and again stirred (15 min). Solids were removed by suction filtration through Celite. The filter cake was washed with ether (60 mL), the filtrate was shaken in a separatory funnel, the layers were separated, and the aqueous phase was further extracted with ether (3 × 40 mL). The combined organic layers were washed with water (50 mL), dried, and concentrated. The residue (650 mg, 92%) was separated by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) into pure **43** and **44** (ratio 1:2).

For **43**: colorless oil; IR (neat, cm^{-1}) 3350, 3060, 2958, 1455, 1360, 1094, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1 H), 4.14 (q, J = 6.4 Hz, 1 H), 1.53 (br, 1 H), 1.74–1.69 (m, 1 H), 2.40 and 1.58 (ABq, J = 3.5 Hz, 2 H), 1.23 (d, J = 6.4 Hz, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.82 (s, 3 H), 0.78–0.61 (m, 2 H), 0.44 (dd, J = 6.0, 3.8 Hz, 1 H), 0.06 (t, J = 3.9 Hz, 1 H); MS, m/z (M^+) calcd 194.1670, obsd 194.1621.

For **44**: colorless oil; IR (neat, cm^{-1}) 3350, 3080, 2990, 2952, 2862, 1465, 1455, 1363, 1090, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 1 H), 4.14 (q, J = 6.2 Hz, 1 H), 1.75–1.69 (m, 1 H), 2.37 and 1.82 (ABq, J = 3.5 Hz, 2 H), 1.25 (d, J = 6.5 Hz, 3 H), 1.03 (s, 6 H), 0.83 (s, 3 H), 0.94–0.61 (m, 2 H), 0.43 (dd, J = 6.0, 3.8 Hz, 1 H), 0.06 (t, J = 4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.82, 127.67, 71.81, 43.68, 38.22, 30.97, 30.69, 29.94, 24.14, 21.99, 19.98, 19.11, 18.80; MS, m/z (M^+) calcd 194.1671, obsd 194.1653.

Diisobutylaluminum Hydride Reduction of 42. A. Dichloromethane Solution. A cold (−78 °C), magnetically stirred solution of **42** (2.45 g, 12.8 mmol) in dry dichloromethane (125 mL) was treated dropwise with 33.5 mL of Dibal (1 M in hexane) during 1.5 h. The reaction mixture was stirred for 30 min and then quenched with water. The product was extracted into dichloromethane (3×), and the combined organic layers were dried and concentrated. MPLC separation of the allylic alcohols (ratio 12:88) as described above furnished the pure isomers **43** and **44** in a combined yield of 83% (2.05 g).

B. Ether Solution. Reduction of a cold (−78 °C), magnetically stirred solution of **42** (47 mg, 0.245 mmol) in dry ether (3 mL) with 0.64 mL of Dibal (1 M in hexane) as described above furnished 36 mg (76%) of an identical 12:88 mixture of **43** and **44**.

Ethyl (1*R,2*R**,7*S**)-3-[(*E*)-Ethylidene]-1,5,5-trimethylbicyclo-[5.1.0]octane-2-acetate (49a).** A solution of **43** (35.8 mg, 0.185 mmol) and triethyl orthoacetate (0.36 mL) in xylene (1 mL) containing 1.8 μL of propionic acid was heated at the reflux temperature under nitrogen for 2 h. During this time, the progress of reaction was carefully monitored by VPC and TLC. The cooled reaction mixture was diluted with ether (10 mL), and this solution was washed successively with 10% hydrochloric acid (5 mL), saturated sodium bicarbonate solution (2 × 5 mL), and brine (5 mL). Drying and solvent evaporation gave pure **49a** (41 mg, 84%) as a colorless oil: IR (neat, cm^{-1}) 3062, 2960, 1764, 1460, 1380, 1374, 1287, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (q, J = 6.5 Hz, 1 H), 4.09 (q, J = 6.0 Hz, 2 H), 2.48–2.43 (m, 3 H), 2.13 (t, J = 8.1 Hz, 1 H), 1.84–1.78 (m, 1 h), 1.61 (d, J = 6.5 Hz, 3 H), 1.52 and 1.26 (ABq, J_{AB} = 2.9 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 0.94 (s, 3 H), 0.88 (s, 3 H), 0.87 (s, 3 H), 0.54 (dd, J = 8.2, 4.0 Hz, 1 H), 0.45–0.41 (m, 1 H), 0.23 (t, J = 4.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.13, 138.32, 117.36, 60.03, 47.46, 46.43, 43.46, 35.58, 35.46, 32.86, 23.96, 22.81, 22.09, 20.79, 18.95, 14.26, 13.20; MS, m/z (M^+) calcd 264.2089, obsd 264.2057.

(1*R,2*R**,7*S**)-3-[(*Z*)-1,5,5-Trimethylbicyclo[5.1.0]octane-2-acetic Acid (49b).** A solution of **49a** (24 mg) and potassium hydroxide (16.4 mg) in 95% ethanol (0.9 mL) was heated at reflux for 2 h, cooled, and evaporated. Workup in the manner described above afforded 20 mg (94%) of **49b** as a colorless solid: mp 114–115.5 °C; IR (CCl_4, cm^{-1}) 3200–2550, 1690, 1385; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (q, J = 6.6 Hz, 1 H), 2.69–2.44 (m, 3 H), 2.16–2.11 (m, 1 H), 1.83 (dq, J = 4.2, 2.1 Hz, 1 H), 1.63 (d, J = 6.9 Hz, 3 H), 1.53 (d, J = 13.3 Hz, 1 H),

1.28–1.20 (m 1 H), 0.95 (s, 3 H), 0.89 (s, 3 H), 0.88 (s, 3 H), 0.57 (dd, J = 6.1, 4.0 Hz, 1 H), 0.49–0.41 (m, 1 H), 0.26 (t, J = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.02, 138.14, 117.50, 47.46, 46.20, 43.45, 35.49, 35.22, 32.84, 23.96, 22.83, 22.15, 20.89, 18.91, 13.24; MS, m/z (M^+) calcd 236.1776, obsd 236.1783.

Ortho-Ester Claisen Rearrangement of 44. A solution of **44** (41 mg, 0.21 mmol) and triethyl orthoacetate (0.41 mL) in xylene (1.1 mL) containing propionic acid (2.1 μL) was heated at reflux under nitrogen for 3.2 h. Following the predescribed workup, there was isolated 40 mg (72.5%) of an inseparable 1:1 mixture of **51a** and **52a**: IR (neat, cm^{-1}) 3060, 2950, 1735, 1460, 1378, 1263, 1158, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (**51a**, q, J = 6.7 Hz, 0.5 H), 5.19 (**52a**, q, J = 7.4 Hz, 0.5 H), 4.16–4.07 (m, 2 H), 2.91–2.70 (m, 2 H), 2.37–2.21 (m, 2 H), 1.87–1.77 (m, 2 H), 1.71 (**52a**, d, J = 7.2 Hz, 3/2 H), 1.59 (**51a**, d, J = 6.8 Hz, 3/2 H), 1.24 (t, J = 7 Hz, 3/2 H), 1.22 (t, J = 7 Hz, 3/2 H), 1.04 (s, 3/2 H), 1.01 (s, 3/2 H), 0.94 (s, 3/2 H), 0.91 (s, 3/2 H), 0.88 (s, 3/2 H), 0.86 (s, 3/2 H), 0.51–0.43 (m, 2 H), 0.26 (s, 1/2 H), 0.22 (s, 1/2 H); MS, m/z (M^+) calcd 264.2089, obsd 264.2061.

Saponification of 29 mg of this mixture as before gave in 93% yield a 1:1 mixture of **51b** and **52b**: MS, m/z (M^+) calcd 236.1777, obsd 236.1800.

(1a*R,7a*R**,7b*S**)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-6*H*-cycloprop[*e*]azulen-6-one (50).** A mixture of acids **49b**, **51b**, and **52b** (ratio 88:6:6, 160 mg, 0.68 mmol) was dissolved in benzene (6 mL), cooled in ice, and treated dropwise with oxalyl chloride (0.68 mL). The reaction mixture was stirred for 1-h intervals at 5 and 20 °C before solvent evaporation. The residue was redissolved in benzene (10 mL), and the concentration process was repeated to give the acid chloride as a brownish oil that was used without further purification.

A cold (−78 °C), magnetically stirred solution of the above material in dichloromethane (60 mL) was blanketed with nitrogen and treated dropwise with 0.04 mL (0.5 equiv) of stannic chloride. After 20 min, an additional 0.08 mL of $SnCl_4$ was introduced, and stirring was continued for 20 min longer. Water was added, and the organic phase was washed with saturated sodium bicarbonate solution and dried. This solution was treated with 10 mL of a 2:1 mixture of dichloromethane and triethylamine and stirred at room temperature for 8 h. Filtration, concentration of the filtrate and MPLC purification on silica gel (elution with 8% ethyl acetate in petroleum ether) afforded in a combined yield of 53% (78 mg) the tricyclic enones **50** and **53** (ratio 94:6).

For **50**: IR (neat, cm^{-1}) 3060, 2960, 1760, 1698, 1640, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 and 2.13 (ABq, J_{AB} = 3.4 Hz, 2 H), 2.50–2.30 (m, 2 H), 1.96 (dd, J = 14.7, 4.7 Hz, 1 H), 1.7 (s, 3 H), 1.35–1.03 (m, 2 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.78 (s, 3 H), 0.69–0.61 (m, 2 H), 0.32 (s, 1 H); ^{13}C NMR 209.43, 173.45, 136.19, 48.86, 46.61, 45.20, 42.32, 38.44, 34.97, 32.16, 27.52, 22.41, 21.91, 19.00, 18.66; MS, m/z (M^+) calcd 218.1671, obsd 218.1669.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.29; H, 10.07.

For **53**: IR (neat, cm^{-1}) 3060, 2960, 1775, 1700, 1640, 1370; ^{1}H NMR (300 MHz, $CDCl_3$) δ (only distinctive signals listed) 1.65 (d, J = 2.0 Hz, 3 H), 1.18 (s, 3 H), 1.17 (s, 3 H), 0.94 (s, 3 H), 0.38–0.34 (m, 1 H), −0.01 (t, J = 4.6 Hz, 1 H); MS, m/z (M^+) calcd 218.1671, obsd 218.1668.

Comparable cyclization of a 1:1:1 mixture of the three carboxylic acids furnished **50** and **53** in a 2:1 ratio.

(1a*R,6*R**,7a*R**,7b*S**)-1a,2,3,4,6,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulen-6-ol (54).** A cold (−78 °C), magnetically stirred solution of **50** (235 mg, 1.08 mmol) in dry dichloromethane (17 mL) was treated dropwise with 2.82 mL of Dibal (1 M in hexane), stirred for 30 min, and treated with water. The product was extracted into dichloromethane (3×), and the combined organic layers were dried and evaporated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 202 mg (85%) of **54** containing ~5% of **55** (NMR analysis): mp 83–85 °C (from hexane); IR (CCl_4, cm^{-1}) 3700, 3058, 2750, 1462, 1380, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (t, J = 5.9 Hz, 1 H), 2.28 (dt, J = 12, 4.0 Hz, 1 H),2.20–2.05 (m, 2 H), 1.97 (d, J = 4.8 Hz, 1 H), 1.79 (dd, J = 9, 4 Hz, 1 H), 1.68 (d, J = 1 Hz, 3 H), 1.52–1.43 (m, 2 H), 1.25 (s, 1 H), 1.00 (s, 3 H), 0.88 (s, 3 H), 0.80 (s, 3 H), 0.67–0.57 (m, 1 H), 0.51 (dd, J = 4, 6 Hz, 1 H), 0.11 (t, J = 4 Hz, 1 H); MS, m/z (M^+) calcd 220.1827, obsd 220.1823.

(1a*R,6*S**,7a*R**,7b*S**)-1a,2,3,4,6,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-6-(*o*-nitrophenylselenyl)-1*H*-cycloprop[*e*]azulene (56).** Tri-*n*-butylphosphine (43.8 μL, 1.6 equiv) was added via syringe to a solution of **54** (24 mg, 0.109 mmol) and *o*-nitrophenyl selenocyanate (37 mg, 1.5 equiv) in 0.6 mL of dry tetrahydrofuran over a 5-min period at 0 °C. The reaction mixture was stirred at this temperature for 5.3 h, allowed to warm to room temperature, and diluted with ethyl acetate (5 mL). This solution was washed with 5% sodium bicarbonate solution and brine, dried, and concentrated. The residual oil was purified by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) to give 24.3 mg (55%) of **56** as a yellow solid: mp 106–107.5 °C (from hexane); IR (CCl_4, cm^{-1}) 3067, 2960, 1740, 1590, 1522, 1463, 1337, 1305, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.2 Hz, 1 H), 7.67 (d, J = 7.2 Hz, 1 H), 7.51 (dt, J = 7.0, 6.8 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 4.42 (d, J = 4.6 Hz, 1 H), 2.45–2.34 (m, 2 H), 2.14–2.03 (m, 3 H), 1.80 (s, 3 H), 1.76–1.75 (m, 1 H), 1.25 (br, 1 H), 1.03 (s, 3 H), 0.89 (s, 3 H), 0.85 (s, 3 H), 0.89–0.66 (m, 1 H), 0.49 (dd, J = 4.7, 8.1 Hz, 1 H), 0.12 (t, J = 3.2 Hz, 1 H); MS, m/z (M^+−2-$NO_2C_6H_4Se$) calcd 203.1800, obsd 203.1834.

(1a*R,4a*R**,5*S**,6*R**,7a*R**,7b*S**)-4a,5-Epoxydecahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulen-6-ol (57).** To a cold (0 °C) mixture of **54** (122 mg, 0.55 mmol), *tert*-butyldimethylsilyl chloride (102 mg, 0.68 mmol), and imidazole (95 mg, 1.4 mmol) was added dry dimethylformamide (1.6 mL) dropwise. After being allowed to warm to room temperature, the mixture was stirred for 5 h and diluted with water and petroleum ether. The aqueous phase was extracted with petroleum ether (3×), and the combined organic layers were dried and concentrated. Purification of the residue by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) afforded 163.5 mg (89%) of silylated ether: IR (neat, cm^{-1}) 3060, 2960, 2868, 1463, 1353, 1265, 1090, 890, 847, 777; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (t, J = 6.3 Hz, 1 H), 2.19–2.13 (m, 2 H), 2.08–1.95 (m, 2 H), 1.76 (dd, J = 4.9, 9.7 Hz, 1 H), 1.62 (br, 3 H), 1.55–1.46 (m, 2 H), 1.01 (s, 3 H), 0.93 (s, 9 H), 0.89 (s, 3 H), 0.78 (s, 3 H), 0.69–0.57 (m, 1 H), 0.49 (dd, J = 4.2, 8.1 Hz, 1 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.07–0.04 (m, 1 H); MS, m/z (M^+) calcd 334.2692, obsd 334.2736.

The silyl product (176 mg, 0.527 mmol) dissolved in dry chloroform (2 mL) was treated with *m*-chloroperbenzoic acid (128 mg, 0.83 mmol) at −20 °C. After the reaction mixture had been stirred for 20 h, solid calcium hydroxide was added, and stirring was continued for 10 min. Filtration and solvent evaporation left a residue (159 mg), the ratio of stereoisomers in which was established by 300-MHz ^{1}H NMR spectroscopy.

For the more polar β-epoxy isomer: IR (neat, cm^{-1}) 3067, 2950, 1470, 1370, 1260, 1080, 845, 780; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (d, J = 6.7 Hz, 1 H), 2.25 and 1.10 (ABq, J = 4.8 Hz, 2 H), 1.86 (dd, J = 14.9, 4.9 Hz, 1 H), 2.07–1.14 (series of m, 4 H), 1.31 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H), 0.82–0.60 (m, 1 H), 0.47 (dd, J = 8.0, 4.4 Hz, 1 H), 0.13 (t, J = 4.4 Hz, 1 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 75.79, 74.15, 69.40, 46.56, 42.34, 40.20, 34.87, 33.47, 31.71, 30.14, 25.82, 22.00, 21.52, 20.27, 18.32, 18.01, 12.75, −4.47, −5.04; MS, m/z (M^+) calcd 350.2641, obsd 350.2620.

For the less polar α-epoxy isomer: colorless solid; mp 106–108.5 °C (from hexane); IR (CCl_4, cm^{-1}) 3070, 2958, 1474, 1370, 1255, 1113, 892, 843; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (m, 1 H), 1.99–0.86 (series of m, 7 H), 1.24 (s, 3 H), 1.15 (s, 3 H), 1.13 (s, 3 H), 0.92 (s, 12 H), 0.84–0.66 (m, 1 H), 0.55 (dd, J = 8.4, 4.3 Hz, 1 H), 0.13 (t, J = 4.7 Hz, 1 H), 0.08 (s, 3 H), 0.07 (s, 3 H); MS, m/z (M^+−C_4H_9) calcd 293.1936, obsd 293.1942.

The unpurified epoxy silyl ether mixture (159 mg) was dissolved in dry tetrahydrofuran (2 mL) and treated with tetra-*n*-butylammonium fluoride (1.36 mL of 1 M in THF, 3 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 7 h. Water and ether were added, and the organic phase was dried and concentrated. The residue was purified by MPLC on silica gel (elution with 21% ethyl acetate in petroleum ether) to give pure samples of **57** and **58** (ratio 60:40; combined yield 66.8%).

For **57**: 50 mg; oil; IR (neat, cm^{-1}) 3464, 3063, 2980, 1470, 1390, 1230, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (d, J = 7.1 Hz, 1 H), 2.24 and 1.10 (ABq, J = 4.7 Hz, 2 H), 2.16–1.84 (m, 3 H), 1.69–1.54 (m, 2 H), 1.38 (s, 3 H), 1.24–1.14 (m, 1 H), 1.02 (s, 6 H), 1.00 (s, 3 H), 0.72–0.62 (m, 1 H), 0.50 (dd, J = 8.0, 4.5 Hz, 1 H), 0.15 (t, J = 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 75.63, 73.95, 68.94, 46.46, 42.30, 40.12, 34.54, 33.54, 31.66, 30.14, 21.74, 21.56, 20.18, 17.99, 12.27; MS, *mz* (M^+) calcd 236.1776, obsd 236.1783.

For **58**: 33 mg; colorless solid, mp 127–129 °C (from hexane); IR (CCl_4, cm^{-1}) δ 3460, 3060, 2960, 1470, 1452, 1385, 1265, 1053, 730, 710; ^{1}H NMR (300 MHz, $CDCl_3$) 3.92 (t, J = 6.2 Hz, 1 H), 2.06–1.92 (m, 2 H), 1.68–1.59 (m, 3 H), 1.49–1.37 (m, 2 H), 1.31 (s, 3 H), 1.28–1.23 (m, 1 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 0.92 (s, 3H), 0.76–0.69 (m, 1 H), 0.55 (dd, J = 4.1, 8.4 Hz, 1 H), 0.14 (t, J = 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 75.65, 70.41, 65.98, 46.51, 45.32, 42.65, 33.34, 31.49, 25.05, 24.38, 23.18, 22.86, 17.46, 12.73; MS, m/z (M^+) calcd 236.1776, obsd 236.1762.

(1a*R,4a*S**,5*R**,6*R**,7a*R**,7b*S**)-4a,5-Epoxydecahydro-3,3,5,7b-tetramethyl-1*H*-cycloprop[*e*]azulen-6-ol (58).** A mixture of **54** (11 mg, 0.05 mmol), *tert*-butylhydroperoxide (6.9 μL of 72% aqueous solution,

1.1 equiv), and $VO(acac)_2$ (1 mg) in benzene (0.25 mL) was stirred at room temperature under nitrogen for 17 h and heated at the reflux temperature for 2 h. The reaction mixture was diluted with benzene and successively washed with saturated sodium bicarbonate solution and brine. After drying and solvent removal, the crude product was purified by MPLC on silica gel (elution with 23% ethyl acetate in petroleum ether) to give 7 mg (59%) of pure **58**. The spectra of this material were identical with those reported above.

(1a*R,4a*R**,7a*R**,7b*S**)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-4a*H*-cycloprop[*e*]azulen-4a-ol (59).** Methanesulfonyl chloride (42 μL, 2 equiv) was added dropwise to a magnetically stirred solution of **57** (62 mg, 0.263 mmol) and triethylamine (73 μL, 2 equiv) in 3 mL of dichloromethane at −20 °C. After 2 h, water and dichloromethane were added, and the separated organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine. Drying and solvent evaporation gave the epoxy mesylate as a white solid (93 mg) that was used directly in the next step.

A solution of this solid in dry tetrahydrofuran (1.5 mL) was added to liquid ammonia (30 mL), and 9.1 mg (5 equiv) of lithium wire was added in three pieces. When the reaction mixture turned colorless (ca. 2 h), another 9.1 mg of lithium wire was introduced. After 3 h, solid ammonium chloride was carefully added followed by 20 mL of hexane. Stirring was continued for 2 h, water was added, and the layers were separated. The aqueous phase was extracted with ether, and the combined ethereal solutions were washed with water and brine, dried, filtered, and concentrated. Purification by column chromatography (alumina activity III, elution with 3.8% ethyl acetate in petroleum ether) returned 41 mg of **57** and gave 12 mg of **59** (61% based on recovered starting material): IR (neat, cm^{-1}) 3600–3465, 3062, 2964, 1464, 1387, 1367, 1025, 990, 900, 820; ^1H NMR (300 MHz, C_6D_6) δ 5.21 (m, 1 H), 2.38–2.29 (m, 1 H), 2.16–2.11 (m, 1 H), 1.87 (d, J = 7.4 Hz, 1 H), 1.79–0.57 (series of m, 6 H), 1.57 (m, 3 H), 1.37 (s, 3 H), 1.03 (s, 3 H), 0.76 (z, 3 H), 0.40 (dd, J = 3.9 Hz, 1 H), 0.16 (t, J = 4.5 Hz, 1 H); MS, m/z (M^+) calcd 220.1827, obsd 220.1833.

Africanol (1). Allylic alcohol **59** (8 mg, 0.036 mmol) in ethyl acetate (1.5 mL) containing 6 mg of platinum oxide was shaken under 50 psi of hydrogen for 3 days. The mixture was filtered, and the filtrate was evaporated. MPLC purification on silica gel (elution with 3.8% ethyl acetate in petroleum ether) gave 7 mg (88%) of **1** as a colorless solid, mp 46–47 °C (lit.[11] mp 47–48 °C): IR (CCl_4, cm^{-1}) 3480, 3078, 2965, 1460, 1388, 1266, 1109, 1088, 1024, 993; ^1H NMR (300 MHz, C_6D_6) δ 1.99–1.25 (series of m, 11 H), 1.22 (s, 3 H), 1.02 (s, 3 H), 0.85 (s, 3 H), 0.76 (d, J = 7.4 Hz, 3 H), 0.73–0.60 (m, 1 H), 0.45 (dd, J = 8.5, 3.9 Hz, 1 H), 0.16 (t, J = 4.4 Hz, 1 H); MS, m/z (M^+-H_2O) calcd 204.1878, obsd 204.1862.

(1a*R,4a*S**,7a*R**,7b*S**)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-4a*H*-cycloprop[*e*]azulen-4-ol (60).** Methanesulfonyl chloride (27 μL, 0.34 mmol) was added dropwise to a cold (−20 °C), magnetically stirred solution of **58** (40 mg, 0.169 mmol) and triethylamine (47 μL, 0.34 mmol) in dichloromethane (2 mL). After 1.5 h, water and dichloromethane were added, and the organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine. After drying and concentration, the oily epoxy mesylate (58.8 mg) was used directly in the next step.

To 20 mL of liquid ammonia was added a solution of the above material in 1 mL of dry tetrahydrofuran, followed by 5.9 mg (5 equiv) of lithium wire in three pieces. When the reaction mixture turned colorless (ca. 1 h), an additional 5.9 mg of lithium wire was introduced. After an additional hour, solid ammonium chloride was carefully added followed by 20 mL of hexane. This mixture was stirred for 2 h and treated with water. The aqueous phase was extracted with ether, and the combined organic phases were washed with water and brine, dried, filtered, and concentrated. Purification of the residue by column chromatography (alumina activity III, elution with 2.5% ethyl acetate in petroleum ether) furnished 24 mg (64.5%) of **60** as a colorless oil that crystallizes in the freezer: IR (neat, cm^{-1}) 3600–3465, 3070, 2936, 1455, 1380, 1067, 892, 824; ^1H NMR (300 MHz, C_6D_6) δ 5.30 (br, 1 H), 2.34–2.31 (m, 1 H), 2.01–0.76 (series of m, 7 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.41 (s, 3 H), 1.20 (s, 3 H), 0.87 (s, 3 H), 0.51–0.42 (m, 2 H), 0.13 (t, J = 4.2 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 146.29, 127.00, 86.41, 52.45, 52.30, 44.53, 35.41, 34.55, 30.72, 26.22, 25.45, 23.17, 22.27, 18.24, 11.99; MS, m/z (M^+-H_2O) calcd 202.1721, obsd 202.1700.

(1a*R,4a*R**,5*R**,7a*R**,7b*S**)-Decahydro-3,3,5,7b-tetramethyl-4a*H*-cycloprop[*e*]azulen-4a-ol (61).** Allylic alcohol **60** (21 mg, 0.095 mmol) in ethyl acetate (3 mL) containing 10 mg of platinum oxide was shaken under 50 psi of hydrogen for 24 h. The mixture was filtered, and the filtrate was evaporated. MPLC purification on silica gel (elution with 4.5% ethyl acetate in petroleum ether) gave 19 mg (90%) of **61**; IR (neat, cm^{-1}) 3620, 3080, 2970, 1460, 1170, 1055; ^1H NMR (300 MHz, C_6D_6) δ 2.05–0.71 (series of m, 11 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 0.83 (s, 3 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.54 (s, 1 H), 0.50 (dd, J = 8.3, 3.6 Hz, 1 H), 0.11 (t, J = 4.2 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 84.22, 54.81, 52.43, 46.53, 44.16, 35.29, 34.13, 30.57, 25.50, 25.45, 23.83, 23.67, 22.97, 18.33, 12.81; MS, m/z (M^+) calcd 222.1984, obsd 222.1973.

Acknowledgment. Financial support of this research by the National Institutes of Health (Grant GM-30827) is gratefully acknowledged. We also recognize the early contributions of Drs. David Dime and Kenneth Stevens to this project. The X-ray crystal structure analyses performed by Professor I. Bernal and Dr. James P. Springer were most instrumental in bringing the total synthesis to successful fruition. Dr. Kurt Loening of Chemical Abstracts Service is thanked for his assistance with nomenclature.

Control of Relative Stereochemistry in the Cycloadditive Route to β-Hydroxy Carbonyls. Regio- and Stereoselective Exo Alkylation of Δ^2-Isoxazolines

Dennis P. Curran*[1] and Jyh-Chyang Chao

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received October 30, 1986. Revised Manuscript Received January 12, 1987*

Abstract: The regio- and stereoselective generation and subsequent alkylation of exo-lithiated Δ^2-isoxazolines are reported. Treatment of 3-ethylisoxazoline **4** with lithium diethylamide (8 h, −80 °C), followed by benzyl bromide quench, provided **7d** as a single stereoisomer. A variety of isoxazolines derived from both *cis* and *trans*-olefins undergo similar diastereoselective alkylations. A model is proposed to account for the observed selectivities based on selective (*Z*)-azaenolate formation followed by alkylation on the face opposite from the 4-substituent on the isoxazoline ring.

The synthetic equivalence of Δ^2-isoxazolines (**1**) and aldol adducts (**2**, β-hydroxy ketones) has led to the emergence of a cycloadditive strategy for formation of β-hydroxy carbonyls,[2,3] formerly available only by carbonyl addition routes. In this

0002-7863/87/1509-3036$01.50/0